A Multidisciplinary Lifestyle Intervention for Childhood Obesity:

Effects on body composition, exercise tolerance, quality of life and gut hormones

Rimke C. Vos

Promotiereeks HagaZiekenhuis

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“Wees volwassen, maar blijf altijd een beetje kind” (mijn vader)

Opdracht: voor David, mijn ouders en Floris

Contents

Chapter 1

General introduction

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1 General introduction

Background

Management of childhood obesity and its related health risks consume more and more time of the health professionals. This has led to a challenge for pediatric health care in the field of prevention and treatment of this growing health burden.

The term obesity refers to an excess of adipose tissue or body fat (1). Methods for an accurate and reliable measurement of excess body fat, such as underwater weighing, magnetic resonance imaging or dual energy X-ray absorptiometry, are expensive, time consuming and impractical in general clinical practice (1). Therefore, the body mass index (BMI = weight in kg/(height in m)^2, based on the reliable and easily obtainable measurements of body weight and height, has been proposed to define childhood obesity. The adult cut-off values of BMI for overweight and obesity are 25 and 30 kg/m^2, respectively, and are related to increased risk for morbidity and mortality (2). However, in children these cut-off values are age- and gender dependent. Therefore the working group on childhood obesity of the International Obesity Task Force (IOTF) determined cut-off values for overweight and obesity in children based on 6 large growth studies (3). Using the standard definition for obesity from the 2004 IOTF report, the worldwide prevalence of children with obesity aged 5-17 years was estimated at 2-3% (4). This worldwide estimation is comparable with the 2003 childhood obesity prevalence rate of the Fourth National Growth Study in the Netherlands (5). Of growing concern in this respect are the results of the latest national growth study in the Netherlands (2010), in which the trend of increasing weight is still continuing, whereas the historically ongoing trend to increase height in Dutch children appears to have come to an end (Schonbeck et al, in preparation).

The prevalence rate of childhood obesity is influenced by several factors, including socioeconomic status (SES), ethnicity and gender. In industrialized countries an inverse association between SES and the prevalence rate of childhood obesity has been reported (6). In developing countries overweight is more prevalent in children with higher SES, although there are indications for a shift towards the poor (4;7). Differences in obesity prevalence rates are present also between ethnic groups within a country, with the highest prevalence rate found among children of Turkish and Maroccan origin in the Netherlands (8). In general, the prevalence of obesity tends to be higher in girls compared to boys. In the 1997 nation-wide growth study in the Netherlands the prevalence of obesity in girls was 3.3% compared to 2.6% in boys (5).

Our modern lifestyle has been termed the 'toxic environment', as it promotes high-energy intake by calorie-dense foods and discourages energy expenditure due to changes in means of transportation and leisure time activities. Also the size of food portions has increased over the years and the introduction of sweetened soft drinks has not been helpful either in keeping the body weight between normal boundaries. It has been estimated that each additional serving of sugared soft drinks leads to a 0.24 unit increase in BMI and an increased odds of 1.6 for developing overweight (9).

The current recommendation for treatment of obesity in children is a multidisciplinary lifestyle intervention with parental involvement (10). For obese adolescents one can consider adding a registered drug to the lifestyle intervention, although with caution and under strict follow-up. These recommendations are based on a Cochrane review,

in which 64 studies (54 lifestyle intervention studies and 10 on drug treatment) were included. However, information on long-term outcome (follow-up period of ≥ 6 months after treatment) of obesity treatment in children was limited and in the Cochrane review it was advised to study the efficacy of such approach in a long-term randomized clinical trial design. Also high quality research that considers psychosocial determinants of successful lifestyle interventions are needed to improve the clinician-family interaction (11).

Childhood obesity has a major impact on somatic as well as psychosocial health. Although most obese children will not experience the complications of their excess body weight during childhood, proof of the metabolic consequences may be already evident during those years (12). In fact, over the past few years there are only a few organ systems reported not to be affected by adiposity in children (4;12-14). Adolescent obesity is not only an independent predictor for adult obesity (15), but there is also evidence that the BMI during these years is a stronger predictor for adult morbidity than adult BMI (12). Indeed, the epidemic proportions of childhood obesity suggest that without firm actions in the prevention and treatment of obese children, the health and social consequences will be substantial and long-lasting (12).

Rationale for this thesis

In this thesis the effect of a family-based multidisciplinary cognitive behavioral treatment compared to standard care on obesity and associated complications is evaluated. The effect evaluation of the treatment will be focused on changes in:

- total obesity, defined by the standard deviation score of body mass index;
- abdominal obesity, defined by the standard deviation score of the waist circumference;
- physical fitness, defined by maximal oxygen uptake;
- glucose homeostasis and inflammatory state;
- pre- and postprandial responses of the gastrointestinal hormones ghrelin, PYY and GLP-1; and
- Health Related Quality of Life, both by child and parent report.

Subsequently, the metabolic consequences of childhood obesity on increased health risk are addressed. A model for predicting increased insulin resistance is developed, using the individual parameters of the Metabolic Syndrome, taking into consideration the different impact of the standardized components of the MS.

Outline of this thesis

In *chapter 2* the protocol description is provided of the studies discussed in this thesis, as well as an elaborate description of the family-based multidisciplinary cognitive behavioral treatment provided to the obese children. The effect of this lifestyle intervention compared to standard care on both total and central adiposity, as well as metabolic parameters, inflammatory state and physical fitness is described in *chapter 3*. *Chapter 4* reports on the treatment effect on the pre- and postprandial responses of several gastrointestinal hormones (ghrelin, PYY, GLP-1) related to appetite regulation in the obese children. The effect of obesity and our lifestyle intervention on Health Related Quality of Life is presented in *chapter 5*. Shortcomings of the definition of the Metabolic Syndrome in its current dichotomous form and an alternative method to include the individual components of this syndrome for predicting insulin resistance are described in *chapter 6*. Finally, a brief overview of the major findings and limitations of the work presented in this thesis is given in *chapter 7*. Also the clinical relevance and future implications are discussed.

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Chapter 2

The effect of family-based multidisciplinary cognitive behavioral treatment in children with obesity: study protocol for a randomized controlled trial

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Trials, in press.

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2 The effect of family-based multidisciplinary cognitive behavioral treatment in children with obesity: study protocol for a randomized controlled trial

ABSTRACT

Background

The prevalence of childhood obesity has increased rapidly during the last three decades in the Netherlands. It is assumed that mainly environmental factors have contributed to this trend. Parental overweight and low social economic status are risk factors for childhood obesity. Childhood obesity affects self-esteem and has negative consequences on cognitive and social development. Obese children tend to become obese adults, which increases the risk for developing cardiovascular complications, type 2 diabetes mellitus, and psychosocial problems. Additionally, the secretion of several gastrointestinal hormones, responsible for appetite and food intake, is impaired in obese subjects. Weight reduction through lifestyle changes in order to change health risks is, until now, suggested as the preferred treatment for childhood obesity.
The objective of this study is the effect evaluation of a family-based cognitive behavioral multidisciplinary lifestyle treatment. The intervention aims to establish long-term weight reduction and stabilization, reduction of obesity-related health consequences and improvement of self-image by change of lifestyle and learning cognitive behavioral techniques.

Study design/ Methods

In this randomized clinical trial newly presented children with obesity (8-17 years old) are divided, by randomization, in an intervention and control group, both consisting of 40 obese children. The intervention is carried out in groups of 8-11 children, and consists of respectively 7 and 5 separate group meetings for the children and their parents and 1 joint group meeting of 2½ hours. Main topics are education on nutrition, self-control techniques, social skills, physical activity and improvement of self-esteem. The control group is given advice on physical activity and nutrition. For normal data comparison, data were collected of 40 normal-weight children, 8-17 years old.

Discussion

Because of the increasing prevalence of childhood obesity and the impact on the individual as well as on society, prevention and treatment of obesity in children is of great importance. For evaluation of short- and long-term effects of the treatment, measurements are taken before and after 3 months of treatment, and after 12 and 24 months follow-up. During these visits clinical and biochemical data are determined, cardiovascular fitness tests are performed and quality of life questionnaires are completed.

Trial registration

International Standard Randomised Controlled Trial Number Register ISRCTN36146436

2 The effect of family-based multidisciplinary cognitive behavioral treatment in children with obesity: study protocol for a randomized controlled trial

Background

During the last three decades the prevalence of childhood obesity has increased dramatically in western countries, including the Netherlands [1-7]. In the Netherlands the highest prevalence of obesity is found in children and adolescents of Turkish and Moroccan origin [8,9]. Other risk factors for developing obesity include parental overweight or obesity, low socio-economic status, and low parental education level [4,9-11].

The adult cut-off values of BMI for overweight and obesity are 25 and 30 kg/m^2, respectively, and are related to increased risk for morbidity and mortality [1]. However, in children BMI is age and gender dependent, so that BMI is usually expressed as standard deviation score (SDS). The working group on childhood obesity of the International Obesity Task Force (IOTF) determined cut-off lines for overweight and obesity in children based on the BMI-SDS that ended at 25 and 30 kg/m^2, respectively, at 18 years of age, obtained from 6 large growth studies carried out before the obesity epidemic [2].

The rapidly increasing prevalence of childhood obesity seen during the last few decades, is mostly the result of an increased food consumption and a change from a more physically active lifestyle to a more sedentary one. Studies indicate that 50% of the children and 80% of the adolescents with obesity will remain obese in their adult life [12-14]. In adults obesity is associated with a higher risk for developing type 2 diabetes mellitus and cardiovascular disease [15-19] and in children obesity is associated with increased prevalence of hypertension, dyslipidemia and impaired glucose metabolism [20-27]. The clustering of these risk factors is called the Metabolic Syndrome (MS) also known as Syndrome X or the Insulin Resistance Syndrome [28].

For adults various definitions of the MS have been described. The most commonly used definitions are those proposed by the World Health Organization [29], the National Cholesterol Education Program's Adult Treatment Panel III [30] and the International Diabetes Federation [31]. These three definitions concur for the essential components (central obesity, hypertension, impaired HDL-cholesterol (HDL), triglycerides (TG) and impaired glucose tolerance). For the pediatric age group several definitions have been proposed, but modifications of the three mentioned definitions for adults are used most often [32-38]. However, consensus on the cut-off levels of the components of the MS for pediatric patients is even more difficult to obtain than for adult patients. One of the reasons may be that in children these cut-off levels are not only influenced by gender and ethnicity, but also by age and pubertal stage. In order to get better insight in the impact of the MS in the pediatric age group an internationally accepted definition is necessary.

Moreover, it has become clear that the adipose tissue is an endocrine organ [39,40]. It does not just serve as a fat deposit but it secretes a wide range of hormones and other proteins. Obesity represents a chronic state of inflammation, with increased levels of the C-reactive protein (CRP) [41-43] and decreased levels of adiponectin [44-47]. This chronic state of inflammation may be the common soil for the development of insulin resistance and cardiovascular disease. It has been shown that obese subjects, both adults and children, have significantly lower levels of adiponectin compared to normal weight individuals [44-49]. After clinically relevant weight loss, levels of adiponectin increase accompanied by improvement of insulin sensitivity [48,50].

The insulin secretion after consumption of nutrients is regulated by neural and hormonal signals from the gut and the intestine [51,52]. The gastrointestinal tract is the largest endocrine organ responsible for the regulation and signalling response of food intake to the brain [51,52]. Gastrointestinal hormones are the key mediators in these processes of food intake regulation. Several gastrointestinal hormones are impaired in obese persons, including ghrelin [51-56], peptide YY (PYY) [51,52,57-59] and glucagon-like peptide 1 (GLP-1) [52,60-64]. In contrast to many other endocrine hormones, gut hormones have predominantly short-term actions [52].

Ghrelin is a 28 amino acid peptide released from X/A-like cells of the gastric oxyntic glands, and in lower amounts from the small intestine and the hypothalamus [51-53]. Ghrelin is the only gut hormone known to increase food intake. An inverse association is found between circulating levels of ghrelin and BMI, so that obese subjects have lower levels of ghrelin [51-54,65-67]. There is still much uncertainty about the effect of weight loss on the ghrelin response. Some studies found increased ghrelin levels after weight lost [51,52,56], but others could not confirm this finding [56,68].

Both PYY and GLP-1 are synthesised and released after food intake by L-cells of the distal gut [51,52,57,59,69]. For fasting PYY an inverse association is found with BMI, in both adults [51,52] and children [51,52,57,59], whereas no significant association with body weight was found for fasting GLP-1 [52]. Postprandial levels of both hormones [51,52,59] [52,60-64,70] are found to be blunted in obese individuals, and weight loss seems to affect this [59] [52,61,71]. However, the mechanisms underlying the synthesis and release of especially GLP-1 from L-cells are largely unknown.

Besides these physiological changes, obesity also has a huge impact on the psychosocial well-being of the child with obesity [7,72-75]. Obesity is often associated with feeling ugly, lazy, stupid and with low self-control, which results in a negative self-image and, consequently, social isolation of the obese child. This social isolation can aggravate the obesity because the child can use eating as a coping strategy [72,76].

The question which intervention is most effective in treating both the physiological and psychological aspects of childhood obesity has not yet been definitely answered. The recently published update of the Cochrane review 'Interventions for treating obesity in children' [77] included 54 randomized clinical trials on lifestyle interventions, with 36 focusing on (family-based) behaviorally orientated treatment programs. From the 54 included studies on lifestyle interventions, 40 interventions lasted longer than 6 months, 6 of which up to one year and 4 lasting 2 years. The aim of this Cochrane review was to ascertain which intervention is most effective in the treatment of childhood obesity. However, study design, duration of follow up and outcome measures differed significantly in the included studies and it was only possible to give a recommendation. The results of the meta-analysis showed that for the treatment of childhood obesity a behavioral lifestyle intervention, combined with parental involvement, is preferred over standard care or self-help.

The intensity of the intervention appears important for the efficacy, because an observational study, including 129 treatment centers in Germany, Austria and Switzerland [78] demonstrated a significantly positive association between BMI-SDS reduction and intensity of the intervention after 24 months follow-up, while there was no association with duration. These authors also found a reduced BMI-SDS in nearly half of the children after 24 months of follow-up, with 25% of them showing a reduction of >0.5 SDS, which has been demonstrated to be clinically relevant [79-81]. Younger children (< 12 years) showed significantly higher success rates at 24 months' follow-up.

A major problem with lifestyle intervention programs is the high percentage of incomplete follow-up data due to drop-out or lack of documentation, which makes it very difficult to reliably assess the effectiveness of the treatment. Therefore, in order to accomplish long-term weight loss and health improvement, future research should focus on adequately powered long-term (> 6 months) evaluation of lifestyle interventions, with psychosocial determinants for behavioral change and parental involvement.

Objective

The primary aim of this study is the effect evaluation of a family-based multidisciplinary cognitive behavioral treatment on obesity (expressed as body mass index (BMI)-standard deviation score (SDS)) compared to standard care (advice on increased physical activity and dietary changes) in children with obesity. The secondary aim of the study is to investigate the effect of this treatment on changes in waist circumference, insulin sensitivity, inflammation, secretion of gastrointestinal hormones and changes in physical fitness and quality of life, compared to standard care. Furthermore, we aim at assessing the effects of possible predictive factors for the long-term response to treatment.

Main research question

1. Do children (8-17 yr.) with obesity show a significant decrease (> 0.5) in BMI-SDS (as defined by Cole et al. [82]) after 3 months of intensive treatment compared to children who were given advice on increased physical activity and dietary changes?

Secondary research questions

1. Do children with obesity have significantly more beneficial effect of 3 months intensive treatment compared to standard care on changes in waist circumference, insulin sensitivity, secretion of gastrointestinal hormones, cardiovascular fitness and quality of life?
2. Will the hypothesized beneficial effects of 3 months intensive treatment in children with obesity persist after 12 and 24 months of follow-up?
3. Are ethnic background of the children, the level of parental education, or the socio-economic status predictive variables for the degree of obesity in these children, and for the success of treatment?

METHODS/DESIGN

Design

The study design is a randomized clinical trial for 2 years.
Newly presented children with obesity referred to the pediatrician are physically examined. If a child meets the inclusion criteria of the study, the pediatrician informs the parents and the child about the study. After written informed consent, the children are randomized to the intervention and control group, after stratification for gender and ethnicity, in two age groups, one from 8 to 12 years and one from 13 to 17 years. An experienced assistant blinded for the study design measures weight and height.

Ethnicity is determined according to self-reports by the parents. For this analysis children are classified as 'Northern European' if both parents report the Northern European ethnicity, and 'Others' if one or both parents report another ethnicity.

To enable comparison of the participants' anthropometric and biochemical data with proper reference data, an age-matched sample of healthy children with normal weight is recruited from the youth health services (Jeugd GGD Haaglanden).

Measurements are taken before (t=0 months) and after (t=3 months) the treatment of the intervention group and after a follow-up period of 12 months. For long-term purposes the intervention group is also evaluated after 24 months. The control group is offered the same treatment regimen after 12 months.
The normal weight control group is measured once.

Eligibility criteria

Children with obesity (according to Cole et al. [2]) aged 8-17 years, living in the Hague and in the area around the Hague and referred to a pediatrician, are invited to participate. Reasons for referral are overweight or obesity, and increased risk of co-morbidity (e.g. hypertension, family history of diabetes mellitus and/or hypercholesterolemia and/or cardiovascular disease before the age of 55, Hindustani ethnicity).
Potential participants are excluded if their knowledge of the Dutch language, intelligence or social skills are insufficient to participate in the group. Other exclusion criteria are use of medication that might have an effect on weight loss, medical co-morbidities that could affect participation, or previous enrollment in another cognitive behavioral treatment program with the focus on reducing obesity.

Recruitment

During the first pediatric consultation inclusion and exclusion criteria are checked. Motivation and expectations of both children and parents are evaluated; e.g. it is checked whether they understand the reason to participate and know why it is important to reduce body weight, and whether their expectations of the treatment are realistic. Pros and cons of treatment versus no treatment are discussed, as well as alternative treatment options. If the children do not fulfill the inclusion or exclusion criteria an alternative treatment is offered to the parents and the child.

Randomization

For the children who meet the inclusion criteria the parents and the children are asked to sign the informed consent. Following informed consent of all participating children and parents the children are stratified by gender and ethnicity ('North European' and 'Other') and randomized to the intervention or control group according to coin-tossing. In order to obtain a similar size of the intervention and control groups, blocked randomization is applied with an allocation ratio of 1:1. Randomization is carried out by a member of the team who does not take part in the treatment. Both the intervention and control groups consist of 40 children per group. The children in the intervention group are divided into smaller groups of 10, depending on the child's age. After randomization, children receive a randomization code. All data are analyzed according to this randomization code. The key to the source data is only known by the researcher and research coordinator. The researcher is familiar with the study procedure, is trained prior to the study and collects all data for this study. The normal-weight control group consists of 40 children, 8-17 years, with normal body weight.

Ethic Aspects

This study is conducted in agreement with the 'Declaration of Helsinki'.
Approval is obtained from the regional medical ethical committee Zuid-West Holland.
All parents and children gave their written informed consent.

TREATMENT

Treatment Intervention group

The cognitive behavioral treatment program consists of an intensive phase of three months, followed by booster sessions for a total period of two years. During the intensive phase of the program the intervention group is offered 7 group meetings of 2½ hour and the parents are offered 5 separate parent meetings and 1 meeting together with the children.
The primary goal of the cognitive behavioral treatment is recognition and acknowledgement of the obesity and learning a healthy lifestyle. This is accomplished by health education and by teaching cognitive behavioral techniques.
The secondary goals of the treatment program are a reduction of 10% of the body weight during the intensive phase of the treatment and a further reduction or at least maintenance of the reduced body weight.
A treatment period of at least two years is chosen because it will take time to adapt to a new lifestyle and the risk of relapse is considerable.

Screening phase

During the screening phase the children with their parents are seen at two separate occasions individually by a dietitian, a child-physiotherapist, a child-psychologist and a social worker. In this way it is evaluated whether the timing of the treatment is appropriate, and whether there are individual family situations which could interfere with the treatment. Also causal factors of the obesity are discussed and opportunities to establish lifestyle changes are mapped out.

Dietitian: During the first consultation the weight and diet history of the child and their family are verified. Also their general knowledge of nutrition and their expectations of the role of a dietitian in helping them to reduce body weight are discussed. At the end of the session the child is asked to make a diet report of two weekdays and one weekend day. During the second session an evaluation of the diet reports is made and information is provided about nutrition and healthy eating behavior according to the traffic light nutritional list. The traffic light nutritional list [83] is divided into several main food groups (e.g. fruits, vegetables, grains, milk and other dairy products, meat, fish, and others). Foods within each group are color coded according to the calorie density per average serving and Dutch standards for health nutrition. The colors, similarly to those of a traffic light, are green for "go", orange for "approach with caution", and red for "stop". The goal of the use of the traffic light nutritional list is not only to reduce calorie intake but more importantly to learn healthy eating behavior. At the end of the second session achievable treatment goals are formulated.

Physiotherapist: Current physical activity level and sedentary behavior of the child is reviewed. Energy intake versus energy expenditure is evaluated and visualized for the child by a computer program. With this computer program the child can choose a favorite product from a nutritional list and the program then shows the child the amount of time and intensity of physical activity that is necessary to burn the energy consumed. Also options to change or optimize physical and sedentary activities are debated. The child is advised how to find suitable exercise programs.

Psychologist: Most children with obesity do not have sufficient insight in how obesity develops and how to reduce body weight. The role of the child psychologist is to help the child not only to reduce weight by learning cognitive behavioral techniques, but also to deal with and accept their own body.
For the success of the treatment the children must be motivated and able to change behavior. It is explained that the role of the parents during the treatment is that of 'the therapeutic helper'. The degree of suffering with regards to body image and the role of eating and obesity in the family are evaluated as well.
During the individual consultations by the child psychologist several questionnaires are asked to be filled; the 'Dutch Eating Behavior Questionnaire' (Nederlandse Vragenlijst Eetgedrag/ NVE) [84], the 'Child Behavioral Checklist' (CBCL) [85], the 'Youth Self Report' (YSR) [85], the 'Teacher Report Form' (TRF) [85] and the 'Perceived Competence Scale for Children' (CompetentieBelevenisSchaal voor Kinderen/ CBSK) [86].
Before the child starts with the group sessions individual treatment goals are written down in a contract. It is important that the goals are achievable to avoid disappointment.
Also a buddy is chosen by the child who will help to achieve his or her goals.

Treatment

Group treatment is a useful way to learn cognitive behavioral techniques especially if groups are limited to 8-10 participants. Children can learn from each other (modeling). Peer group support is especially important for the older children group (≥ 12 yrs).
Before the first group session the children receive a treatment manual with the objectives and goals of the treatment and, per session, information about the topics discussed.
To achieve successful treatment results it is important, at the beginning of the treatment, to focus more on the effort to change habits and the input of the participants and less on the weight reduction goals. This is accomplished by making the child aware of its own actions and way of living that has led to his or her obesity.

Several cognitive behavioral techniques are learned (knowledge, skills and attitude) during the intensive phase of the treatment in order to maintain long-term lifestyle change and body weight reduction. The cognitive behavioral strategies are learned during six sessions of 2½ hours per session. Sessions are given biweekly.
Each session contains the following components:

- Determination of body weight
- Homework discussion and evaluation
- Education
- Physical activity
- Role playing
- Discussing homework for next meeting
- Set goals linked to educational topics of the session

Parental Involvement

Not only the motivation to change the lifestyle of the children is important, but also the motivation of the parents. Parents must be willing to invest time in the treatment. Separate parallel parent group sessions (5 evenings) are offered by a dietitian and a social worker. In most cases parents do the shopping and food preparation, so for the treatment to be successful parental involvement and support is essential.
The role of parents is that of 'the therapeutic helper' who gives positive feedback to their children and supports the child in a positive way.
Parents should be a role model for their children, giving a good example through eating healthy food, increasing physical activity and decreasing sedentary activity.

Children's Group Sessions

Educational topics in session 1

Most children with obesity have negative experiences with group activities. For example, they are often not included in social events or chosen last by peers during sport activities. Therefore, during the first session much time is spent in getting acquainted with each other. A good group bond is important for the effect of the treatment because peer support can be very helpful in the treatment of obese children. During this part of the session children give their individual motivation for participating.
The topic of the second part of this session is nutritional information and the balance between energy intake and energy expenditure. This is explained by using the symbol of a balance. Solutions to improve the misbalance are discussed. When the energy intake part of the balance is greater than the energy expenditure part, energy expenditure must be increased or energy intake must be decreased, or both.

Educational topics in session 2

The main topic of the second session of the treatment phase is again information on healthy nutrition. Different categories of nutrition and quantities of each category linked to a healthy eating pattern are discussed. Children learn how to read product labels and to obtain information on misleading advertisement. They also discuss how to deal with meals (breakfast, lunch, diner, 2 healthy snacks), and how to make healthy choices and develop healthy eating habits (small bits, slow eating, eating at the family table, no other activities during eating). In games the educational topics are rehearsed and participants need to label products according to the traffic light method [83].

Educational topics in session 3
In this session self-control techniques to cope with difficult situations are taught. Children formulate and acknowledge difficult situations (e.g. birthday parties, holidays, lunch breaks at school, being at home alone). Problem solving alternatives are debated (e.g. to avoid a situation, doing something else, participate in a situation and eat less, or participate followed by extra exercise afterwards). The problem-solving alternatives are rehearsed with role-playing.
Other psycho-educational topics reviewed during the third session are self-reward (when coping well with a difficult situation) and self-regulation situations (making a plan how to integrate healthy behavior in daily living). Stimulus control is also one of the psycho-educational topics of the third session (remove unhealthy stimuli at home, encourage healthy behavior, eat at the dinner table, reduction of environmental stimuli linked to eating).

Educational topics in session 4
Most people associate obesity with being ugly, lazy or stupid which makes children with obesity often the subject of teasing by peers. The topics of the fourth session are therefore coping with teasing and being teased, how to deal with it and how to react with dignity. The children are explained that there are three coping strategies to deal with this situation; react angry (fight), walk away (flight) or deal with the situation (preferred strategy). Using role-playing the children are taught to react with a dignified, but powerful response. During this session the children are asked to think of someone in their environment who can help them during difficult situations or when they are teased.

Educational topics in session 5
The focus of the fifth session is self-image. Most children with obesity have a low self-image and a low health-related quality of life. Not only other people associate obesity with being ugly, lazy or stupid, but the children also think likewise about themselves. It is difficult for them to mention positive things about themselves. Children are taught to take a positive look at themselves and name positive, nice things or characteristics about themselves and other children in the group.

Educational topics in session 6
During the sixth session the children are given the opportunity to repeat topics discussed during the other sessions. Also cognitive strategies and relapse techniques are taught to maintain newly learned behavior.

Parent Group Sessions

Session 1
Parents are given information on the treatment program of the children and what they can expect of their own group sessions. Information on healthy nutrition, product information, quantities, eating moments, eating locations, how to help their children (also when there are children in the family with a normal body weight) are discussed. Parents also receive advice on parenting styles to give strict rules but also manage the family in a pleasant way.

Session 2
During the second session parents are taught how to support their children during the treatment and thereafter by acknowledging the child's efforts and giving positive feedback. It is made clear to the parents that for the treatment to be a success, parental support is very important.

Session 3
Parenting styles are taught during the third session on how to set boundaries and how to limit the sometimes abnormal eating behavior of their child.

Session 4
During this session topics of the previous sessions are repeated, and questions relevant to the obesity subject are answered.

Session 5
During the last separate parental group session a therapist discusses the role of all other family members with regard to the treatment in the family (e.g. are other family members supportive, how do they cope with the lifestyle changes?).

Joint Session
During the last session children and parents celebrate the end of the intensive period in a healthy way. Children are asked to make healthy snacks and in this way the children can bring into practice how to cope with a normally difficult situation. Games and activities are planned as well, so children and parents can bring into practice that festive parties can also be associated with fun and social interaction instead of the intake of food alone.

Follow-up
Booster sessions are a very important component of the treatment of children with obesity. In order to maintain the newly learned behavior booster sessions are necessary during the first two years. The child psychologist and the social worker organize the booster sessions. The topics that are repeated are: problem solving techniques and relapse prevention techniques.

Treatment Control group
The control group is given an initial physical activity and nutritional advice.
After 12 months the children are offered the multidisciplinary treatment. During the 12 months study period the children are seen at start, after 3 months and at the end of the period just before they start the treatment.

STUDY PROCEDURES

Medical examination
During the first visit to the pediatric clinic general information is collected concerning pregnancy (duration of gestation, smoking, hyperemesis, pre-eclampsy, medication, diabetes) and birth (position of the child during delivery, complications during delivery, birth weight, height, head circumference). Also information on motor and mental development (current educational level) of the child is collected. Furthermore, information on the highest accomplished educational degree and current work of the parents, as well as height, weight and activity level of the parents and other family members and the occurrence of diseases in the family is collected.
At physical examination the occurrence of hirsutism, acanthosis nigricans and possible dysmorphic characteristics is evaluated. Pubertal development is recorded by the pediatrician according to Tanner [87]. Breast development in girls and genital development in boys is used for pubertal classification into two groups. Boys with genital stage 1 and girls with breast stage 1 are classified as prepubertal, and boys and girls with stage 2-5 are classified as pubertal.

Anthropometric parameters

Weight is measured to the nearest of 0.1 kg using an electronic scale (SECA 911, Vogel & Halke, Hamburg, Germany) and height to the nearest of 0.1 cm with a stadiometer (Holtain, limited, Crymych, Dyfed, Britain) in underwear and barefoot. The BMI is calculated as weight / height squared (kg/m2). Subjects are classified as obese using BMI gender- and age specific international cut-off levels developed by Cole et al. [2] BMI expressed as standard deviation score (SDS) for Dutch reference data [82] is used as the main outcome parameter.

Waist circumference (WC, in cm) is measured with an anthropometric tape midway between the lower rib margin and the iliac crest at the end of gentle expiration. The waist to height ratio (WC/Ht) is calculated as WC/height, both measured in centimeters.

Blood pressure measurements (Criton Dinamap, No. 8100) are performed in a relaxed sitting position, in duplicate; the last measurement is used for analyses.

Blood sample analysis

With the participant in the supine position, blood samples are taken by venipuncture after an overnight fast. Before blood sampling, the fasting state is verbally confirmed by the participant and the parent. Fasting blood samples are taken to determine glucose, insulin, C-peptide, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, free fatty acids, free T4, TSH and inflammation parameters (CRP, adiponectin).

Mixed Meal Tolerance Test

The children are asked to consume at least an amount of 150g of carbohydrates three days prior to the mixed meal tolerance test and continue with their normal daily physical activities. The day before the test the children are asked not to consume any food or drinks after 10 pm, with the exception of tap water.
On the morning of the mixed meal tolerance test the fasting state is verbally confirmed by the participant and the parents. An antecubital intravenous catheter is placed for blood sampling. Fasting blood samples are taken twice with an interval of 15 minutes (t=-15 and t=0). After the second fasting blood sample is taken, the participant receives a mixed meal bolus of 200 mL (Nutridrink Yoghurt Style, Nutricia, Zoetermeer, The Netherlands). The mixed meal bolus consists of 49% carbohydrates, 35% lipids and 16% proteins. After the consumption of the mixed meal bolus, blood samples are taken two times with 15 minutes intervals (t=15 and t=30) and four times with 30 minutes interval (t=60, t=90, t=120 and t=150). Blood samples are analyzed and plasma glucose, plasma insulin and gut hormones (Ghrelin, GLP-1, PYY) are determined. In order to be able to analyze levels of the gut hormones GLP-1 and PYY it is necessary to add the enzyme dipeptidyl peptidase IV (DPPIV) to the tubes.

Insulin Resistance and Insulin Sensitivity

An index for insulin resistance is calculated according to the Homeostasis Assessment Model for insulin resistance (HOMA-IR) formula: (fasting insulin (μU/mL) x fasting glucose (mmol/L)) / 22.5 [88].
Insulin sensitivity is calculated using the quantitative insulin-sensitivity check index (QUICKI) formula: 1/(log fasting insulin (mU/L)+log fasting glucose (mg/dl)) [89].

Voluntary Maximal Exercise Test

The physical fitness of the children is determined by a voluntary maximum exercise test on a treadmill using breath-by-breath analysis and plots according to Wasserman [90]. The exercise test consists of three stages; a reference stage (2 minutes rest measurement prior to the exercise test), the test stage (the exercise test till voluntary exhaustion) and a recovery stage (2 minutes recovery measurement in rest after the exercise test). The test stage starts with a velocity of 4 km/h and an angle of 0% during 1 minute. Every minute the velocity is increased with 0.5 km/h and the angle with 2%, till voluntary exhaustion. During the test the participants are encouraged to exert a maximum effort. At the end of the test the children are asked to grade the level of exhaustion by using the Borg scale [91] and the reason to stop.
In adults a maximum effort is achieved when two of the following criteria are fulfilled:

- The difference in heart rate between the last two stages was less than 5 beats per minute.
- The difference in VO_2 was less than 100 mL/min between the last two stages.
- A Respiratory Exchange Ratio (RER) of > 1.0.

However, the first two criteria are not always found in adults and rarely in children. Therefore, in this study peak values are referred to instead of maximum values.
Peak values are reached when the children look physically exhausted and a RER of > 1.0 is accomplished. The physical fitness is calculated from the absolute peak value of oxygen uptake, standardized to age and gender (VO_{2peak}-SDS). Yet the absolute peak oxygen uptake in obese can give an overestimation of the real physical fitness because of their increased body size [90]. For that reason also the peak oxygen uptake adjusted for body weight, age and gender (VO_{2peak}-SDS-kg) is determined to establish a more realistic value for the physical fitness.

Health Related Quality of Life

The health related Quality of Life (HRQOL) of the children is determined by the questionnaires DISABKIDS and KIDSCREEN [92]. The DISABKIDS and KIDSCREEN projects developed an instrument with a generic part (KIDSCREEN), and a chronic generic part (DISABKIDS). The KIDSCREEN part of the questionnaire is suitable for children aged between 8-18 years, and the DISABKIDS part for children aged between 4-18 years. The generic part of the questionnaire is used to compare children with a disease with healthy children. For this part only the child version is used. With respect to DISABKIDS, also the parental version is used, to compare the HRQOL reported by the child with the child's HRQOL from the parents' view.
The KIDSCREEN contains 52 questions divided over 10 subscales of 3-7 items each. The DISABKIDS part of the questionnaire contains 37 questions divided over 6 subscales of 6-7 items each. Every question can be answered by choosing from 5 options: never, almost never/ seldom, average/ sometimes, quite often, always. The items are scored on a 5-point scale (0-4). Both parts are scored by summing the responses for the 52 and 37 items, respectively, after adjustment for the negative items, and expressed as percentages between 0-100. A higher score reflects a better HRQOL.

KIDSCREEN is used to compare the HRQOL of the children with obesity with a normal weight control group and DISABKIDS to compare the obese children in the intervention group with the children in the obese control group. The KIDSCREEN questionnaire has demonstrated a Cronbach α reliability coefficient ranging between .77 and .89 for all ten domains [92]. The Cronbach α reliability coefficient of the child version of the DISABKIDS ranges between .70 to.87 for children aged 8-12 years and between .77 to.90 for children aged 13-16 years [92]. A Cronbach α ≥0.7 is considered as good validity.

Other questionnaires used during the screening phase of the treatment

- *Dutch Eating Behavior Questionnaire (Nederlandse Vragenlijst Eetgedrag/ NVE):*
  The NVE [84] is administered during the screening phase. It consists of three subscales: Emotional Eating (13 items), External Eating (10 items), and Restrained Eating (10 items). The items are scored on a 3-point Likert-type scale ranging from never to very often. The items in the conditional format also have the response option not relevant. A high score reflects a specific eating behavior of the particular subscale. The NVE scales have been proven to provide good internal consistency, satisfactory factorial validity and dimensional stability [72,84].

To assess the child's psychological and social adjustment three versions of the Child Behavior Checklist are asked to fill in. One version is filled in by the parents (Child Behavior Checklist), one by the child themselves (Youth Self Report) and one by a school teacher (Teacher Report Form):

- *Child Behavior Checklist (CBCL):*
  The Dutch version of the CBCL [85] is completed during the screening phase by the parents. The questionnaire includes 138 items and yields scores for total behavior problems, internalizing and externalizing behavior of their child. Also three scores for competence are determined (activity, social competence, school competence)
- *Youth Self Report (YSR):*
  The children fill in the YSR [85] version of the CBCL during the screening phase to visualize the child's own view on his or her internalizing and externalizing behavior.
- *Teacher Report Form (TRF):*
  A school teacher of the child fills in the TRF [85] version of the CBCL in order to determine the internalizing and externalizing behavior of the child at school.
- *Perceived Competence Scale for Children (Competentie Belevings Schaal voor Kinderen/ CBSK):*
  The CBSK [86] is used during the screening phase to determine the self-perception or self-concept of the child. The CBSC consists of 28 items and assesses the child's self-perception in four different areas of perceived competence; cognitive ability, physical activity, peer relations, and general self-esteem.

Type of Analysis

The analyses are performed by using the Statistical Package for Social Science SPSS, v. 17.0 for WINDOWS; SPSS Inc., Chicago, IL, USA) and the level of significance is set to <0.05, according to an intention-to-treat analysis.
Data are checked for normality before analysis using descriptive statistics and histograms. Data are expressed as mean ± standard deviation (continuous variables) and as count and percentage (categorical variables), unless specified otherwise.
For the analysis of treatment effect between both obese study groups for continuous data, independent t-tests, (M)AN(C)OVA and mixed model for repeated measures are used per time point, adjusted for baseline values. Categorical data are analyzed with the Chi-square test for comparison between groups. In addition, paired t-tests, (M)AN(C)OVA and mixed model for repeated measures are used to compare the parameters within treatment groups over time. For predictive analysis linear and logistic regression analysis is used for continuous dependent variables and binomial variables, respectively.

Power Calculation

The sample size of a study was based on the power calculation for unpaired means with normal distribution and can be calculated by the following formula:

$$N_1 = N_2 = (z_{1-\beta} + z_{1-\alpha/2})^2 \times ((\sigma_1^2 + \sigma_2^2) / (\mu_1 - \mu_2)^2)$$

In this study $\alpha = 0.05$ and $\beta = 0.20$ is chosen, so $z_{1-\alpha/2} = 1.96$ en $z_{1-\beta} = 0.84$.
The results of an unpublished pilot study of the proposed treatment given to children with obesity in our hospital showed a clinically relevant difference of 0.6 BMI-SDS between intervention and control group, and the difference between post-treatment and baseline ranged between –2.85 and + 0.70. The difference between the means is therefore chosen as $\mu_1 - \mu_2 = 0.6$ and the estimated sigma, under normality assumption, will be $3.55 / 4 = 0.89$, so $\sigma_1^2 + \sigma_2^2 = 1.58$.
In the formula this determines a $N_1=N_2= 35$. Considering the likely phenomenon of drop-out a $N_1=N_2= 40$ is chosen. The sample size is not adjusted for stratification.

Burden and risks

For evaluation of short-term, midterm and long-term effects of the treatment, measurements are taken at the beginning of the treatment, after 3 months treatment and after 12 (intervention- and control group) and 24 (intervention group only) months of follow-up. During these three (four) visits a physical examination is performed, cardiovascular fitness measured, a mixed meal test performed and blood samples are taken. Children are also asked to complete a quality of life questionnaire.

DISCUSSION

The increasing prevalence of childhood obesity and its impact on individuals and society requires effective preventive programs and therapeutic strategies. The study 'Haagse Maatjes': an effect evaluation of a family-based cognitive behavioral multidisciplinary lifestyle intervention, is a randomized controlled trial with a longitudinal design.
The study aims to establish long-term weight reduction and stabilization, reduction of obesity related health consequences and improvement of the self-image by a change in lifestyle. In order to adjust to a healthy lifestyle, thinking patterns, level of physical activity and eating behavior of the child with obesity and their family must change. For long term-effect of the treatment it is also important that coping strategies and social skills are taught to children with obesity to deal with low self esteem, low self-control and to teach social skills. Also parental involvement and support are necessary for long-lasting, successful treatment results.

We hypothesize that after the intensive treatment period the intervention group will show a significantly lower BMI-SDS compared to baseline and the control group, and that in subjects with a BMI-SDS decrease of more than 0.5, which is considered a clinically relevant weight reduction [79,81,93], a significant health improvement (secondary study outcomes) is attained.

The design of the study is prospective with follow-up measurements at 3, 12 and 24 months. The longitudinal design of the study makes it possible to perform a predictive analysis, rather than only cross-sectional correlations. Furthermore, as mentioned by the authors of the Cochrane review [77], there is an urgent need for interventions with a psychosocial focus for behavioral change and good clinician-family interaction.
We believe that with our study design we do focus on these important aspects.

The children in the intervention group are followed for 2 years and those in the control group for 1 year. Children in the control group are offered the treatment after 1 year, since it is preferable to start treatment of obesity as soon as possible. We expect that some children will drop out of the study during or after the treatment phase. In our power calculation a 10% loss to follow-up was accounted for.

The strength of our study is that, next to the evaluation of the changes in BMI-SDS after intensive lifestyle treatment in obese children, we also assess the effect of weight loss on metabolic health status, inflammation, physical fitness, health-related quality of life and secretion of some gastrointestinal hormones.

The results of this study will provide more insight in the long-term effects of a family-based cognitive behavioral multidisciplinary intervention on weight and BMI-SDS, as well as intended health improvement in children with obesity and their family.

ABBREVIATIONS

BMI = Body Mass Index
BMI-SDS = Body Mass Index Standard Deviation Score
CBCL = Child Behavior Checklist
CBSK = Perceived Competence Scale for Children (CompetentieBelevingsSchaal voor Kinderen)
CRP = C-Reactive Protein
GLP-1 = Glucagon-like peptide 1
HDL-cholesterol = High Density Lipoprotein Cholesterol
HOMA-IR = Homeostasis Assessment Model for Insulin Resistance
HRQOL = Health related Quality of Life
MS = Metabolic Syndrome
NVE = Dutch Eating Behavior Questionnaire (Nederlandse Vragenlijst Eetgedrag)
PYY = Peptide YY
QUICKI = quantitative insulin-sensitivity check index
RER = Respiratory Exchange Ratio
TG = Triglyceride
TRF = Teacher Report Form
VO_{2peak}-SDS= Peak oxygen uptake, adjusted for gender and age
VO_{2peak}SDS-kg= Peak oxygen uptake, adjusted for gender age and body weight
WC = Waist Circumference
WC/Ht = Waist to Height Ratio
YSR = Youth Self Report

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

AUTHORS' CONTRIBUTIONS

All authors are responsible for the design of the study and contributed to the intellectual content of the protocol. RCV was responsible for the implementation of the intervention, data collection, data analysis and drafted the study protocol with suggestions and contribution of all other authors. ECAMH obtained financial support. All authors read and approved the final manuscript.

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Chapter 3

Long-term effect of Lifestyle Intervention on Adiposity, Metabolic Parameters, Inflammation and Physical Fitness in obese children: a randomized controlled trial

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Submitted

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3 Long-term effect of Lifestyle Intervention on Adiposity, Metabolic Parameters, Inflammation and Physical Fitness in obese children: a randomized controlled trial

ABSTRACT

Background
Behavioral lifestyle intervention, combined with parental involvement, is preferred over standard care or self-help in childhood obesity. The short-term results of such interventions are promising, but long-term follow-up results are equivocal.

Objective
The objective of the present study was the short (3 months) and long-term (1 and 2 years follow up) effect evaluation of a family-based multidisciplinary cognitive behavioral lifestyle intervention on markers of adiposity, metabolism, inflammation and physical fitness compared to standard care in children with obesity. Also the association between these outcome variables was determined.

Methods
In this prospective longitudinal clinical trial, obese children were randomly assigned to a 3 months family-based cognitive behavioral multidisciplinary lifestyle treatment (n=40; BMI-SDS 4.2±0.7; age;13.3±2.0yr) or to a control group receiving an initial advice on physical activity and nutrition (n=39; BMI-SDS 4.3±0.6; age 13.1±1.9yr). Anthropometric data, physical fitness, metabolic parameters and inflammatory state were evaluated at baseline, after intervention (at 3 months) and at 1 year follow-up. At 2-year follow-up anthropometric data and physical fitness were measured in the intervention group.

Results
An intervention effect after 1 year was found for adiposity (p=0.02 for BMI-SDS, p=0.03 for WC-SDS), physical fitness (VO_{2peak}-SDS, p<0.01) and insulin resistance (HOMA-SDS, p=0.04). No significant intervention effect was found for serum lipid profile, high-sensitive CRP or adiponectin. At 2 years follow-up BMI-SDS in the intervention group (n=31) was 3.8 ± 1.2 SDS, significantly less than at baseline (p=0.02).

Conclusion
A positive 1 year follow-up treatment effect was found for adiposity, physical fitness and glucose homeostasis, but not for inflammatory markers. There was a significant long-term treatment effect on adiposity, although almost all children remained obese.

Trial Registration
http://www.controlled-trials.com/ISRCTN36146436.

Key words: obesity, children, physical fitness, inflammation, insulin resistance

INTRODUCTION

The rapidly increasing prevalence of childhood obesity observed during the last few decades is assumed to be mostly the result of changes in environmental factors such as urbanization, economic growth, technical changes and culture. These changes have resulted in a large shift both in diet and physical activity patterns. The modern 'Western diet' is high in saturated fats, sugar, and refined foods, but low in fiber. Simultaneously a physically active lifestyle has changed to a more sedentary one (1).

Obesity in childhood tends to persist into adulthood (2-4), and adult obesity is associated with a higher risk for developing type 2 diabetes mellitus and cardiovascular disease (2;4). Moreover, it has become clear that the adipose tissue is not just a fat depot, but also an endocrine organ, producing hormones and inflammation related factors, that contribute to the chronic state of inflammation observed in obesity (5;6). Increased levels of the pro-inflammatory cytokines such as high-sensitive C-reactive protein (hsCRP) (7-9) and decreased levels of adiponectin have been found in children with obesity and insulin resistance (10;11).

An appropriate approach to reduce the obesity related health risks is weight loss. Current treatment recommendations for childhood obesity are lifestyle interventions, including nutritional and physical activity modification guided by social cognitive behavioral techniques (12-14). One of the central assumptions of a cognitive behavioral approach is that higher levels of self-confidence increase the likelihood of lifestyle change (15). In addition, the lifestyle treatment approach has been shown to be equally successful in both clinical, community and school-based settings (13;14;16). Moreover, the results of a recent meta-analysis on lifestyle interventions for obese youth showed that lifestyle interventions lasting for only a few months can be expected to produce significant changes in body weight (13). Also parent involvement in the treatment of obese children showed a clearly beneficial effect on treatment results (13;14). A better treatment result is found when parents are educated about healthy nutrition and when training in behavioral modification was provided (13). Better treatment outcomes have also been observed after group therapy compared to individual treatment only, probably the positive effect of peer support (17). Furthermore, the intensity of the program, defined as more contact time with professional support during the intervention rather than the total duration of the intervention, appears important for its efficacy (18). The results of behavioral lifestyle interventions on adiposity, metabolism, inflammation and physical fitness immediately after treatment are promising (8-10;16;19-23). However, the long-term follow-up effects of such interventions on obesity and associated comorbidity are uncertain (18;24). A younger age at start and a substantial decrease of BMI-SDS during the intervention have been reported to predict a long-term favorable effect (25), but more research is needed to delineate the long-term effects of behavioral lifestyle interventions.

In this paper we report on the short (3 months) and long-term (1 and 2 years) effect of a family-based multidisciplinary lifestyle intervention on markers of adiposity, physical fitness, metabolic parameters and inflammation compared to standard care in obese children.

METHODS

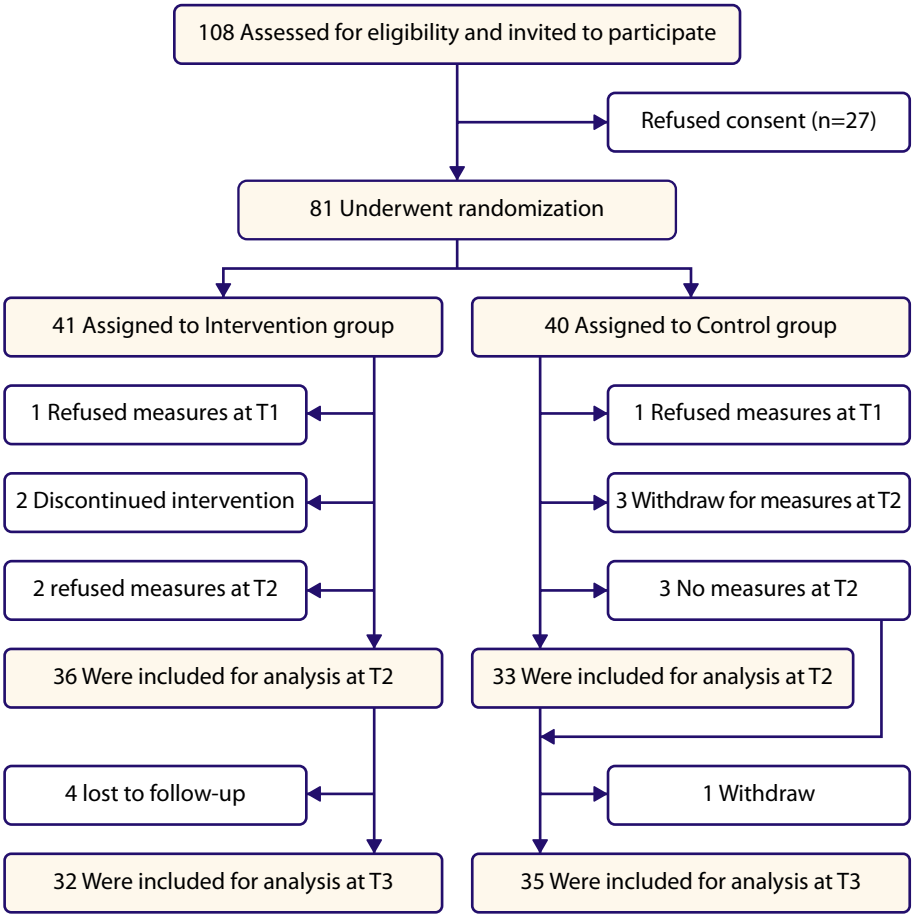
Study Design and Setting

We performed a longitudinal prospective randomized clinical trial to evaluate the effects of a family-based multidisciplinary lifestyle intervention on various clinical and physiological features of obese children (as defined by Cole et al.(26)) aged 8-17 years, who were referred to a pediatric clinic (Juliana Children's Hospital, the Hague). Children who met the inclusion criteria were randomized to receive either a family-based multidisciplinary lifestyle intervention or standard care. Before randomization, stratification took place for age (8-<12 years and 12-<17 years), gender (male vs. female) and ethnicity (North European vs. Others). Normative data for physical fitness, the inflammation parameters and glucose homeostasis were collected from a group of healthy children with a normal body weight recruited by the youth health services (Jeugd GGD Haaglanden). The study was conducted according to the 'Declaration of Helsinki' and approval was obtained from the regional medical ethical committee Zuid-West Holland. All parents and children gave their written informed consent, after they had been given detailed written explanation concerning the aim of the study, discomfort and inconvenience and the option to withdraw at any time.

Participants

Potential participants were excluded if their knowledge of the Dutch language, intelligence or social skills were insufficient to participate in the trial. Other exclusion criteria were use of medication that might have an effect on weight loss, medical co-morbidity that could affect participation or previous enrollment in another cognitive behavioral treatment program with the focus on reducing obesity. Inclusion criteria were simple obesity, 8-17 years and referral to a pediatrician. From the 108 obese children who met the inclusion criteria, 81 agreed to participate. Most given reasons of refusal were: 1) not wanting to take the risk to be randomized to the control group and consequently wait a year before starting treatment; and 2) not wanting to invest the requested time for treatment. Forty-one children were randomized to the intervention group and 40 to the control group (Figure 1). The normal weight control group consisted of 34 healthy, age, gender and ethnicity matched children with normal body weight for height.

Figure 1: *Flow diagram of participants through the study for the primary outcome measure (BMI-SDS)*



Family-based multidisciplinary lifestyle intervention

The family-based multidisciplinary lifestyle intervention of the intervention group consisted of a screening phase of individual counseling of the children with their parents, followed by an intensive phase of group sessions during three months. The group treatment consisted of 7 group meetings for the children, 5 separate parent meetings and 1 parent meeting together with the children. Meetings of 2.5 hours were held once every 2 weeks. The children meetings were held on weekday afternoons at the hospital. The 5 separate parent meetings were provided on weekdays after working hours. Subsequently, refresh follow-up sessions (2-3 sessions/year) were offered for a total period of two years (Table 1).

Table 1: *Characteristics of the Family-based multidisciplinary lifestyle intervention*

Components	Description
Screening phase/ individual counseling	During the screening phase, children and their parents were interviewed at two separate occasions and all individually by the multidisciplinary team consisting of a dietitian, a child-physiotherapist, a child-psychologist and a social worker. Throughout those two separate meetings, an individual advice was given by the multidisciplinary team, based on the personal situation of each participating family.
Individual nutritional advice	A 3-day dietary recall (1 weekend day included) was used by the dietitian to get more insight in dietary habits of the children. Information was provided about nutrition and healthy eating behavior according to the traffic light nutritional list (40). The traffic light nutritional list identifies several main food groups (fruits, vegetables, grains, milk and other dairy products, meat, fish, and others). Foods within each group were color-coded so as to reflect the caloric density per average serving and Dutch standards for healthy nutrition. The colors are green for "go", orange for "approach with caution", and red for "stop". The children and parents were involved in planning their own daily diet for themselves according to the traffic light nutritional list.
Individual physical activity counseling	To obtain insight in the child's general physical activity behavior during the week, a physical activity questionnaire was filled out by a child physiotherapist. Children were asked how they traveled to school (by foot, by bicycle, by public transportation or by car), physical fitness classes at school, spire time sport activities and daily computer and TV use as well as the duration spend at all these activities. The information from this questionnaire was used for advice on how to increase and optimize physical activity during everyday life, such as walking to nearby destinations and reducing sedentary activities (computer and TV use).
Individual psychological counseling	By means of motivational interviewing the child psychologist helped the children to adapting to a new lifestyle in order to reduce body weight. Before the child started with the group sessions individual treatment goals (reduction of 10% of body weight during 3 months group sessions) were written down in a contract to avoid disappointment.
Children's group meetings	Most children with obesity have negative experiences with group activities. For example, they are often not included in social events or chosen last by peer during sport activities. Therefore, during the first session much time is spent in getting acquainted with each other. A good group bond is important for the effect of the treatment because peer support can be very helpful in the treatment of obese children. The main educational focus of the first two meetings is on nutritional information of a healthy eating pattern and the balance between energy intake and energy expenditure. During the subsequent meetings, emphasis was put in self-control techniques to cope with difficult situations (e.g. birthday parties, holidays, lunch breaks at school, being at home alone). Problem solving alternatives are debated (e.g. to avoid a situation, doing something else, participate in a situation and eat less, or participate followed by extra exercise afterwards). Other psycho-educational topics reviewed were self-reward (when coping well with a difficult situation) and self-regulation situations (making a plan how to integrate healthy behavior in daily living). Stimulus control was also one of the psycho-educational topics (remove unhealthy stimuli at home, encourage healthy behavior, eat at the dinner table, reduction of environmental stimuli linked to eating). Topics of the last two meetings were self-image (focus on positive things about themselves) and coping strategies on dealing with teasing.
Parent group meetings	Topics discussed during the parent meetings included the necessity to change their own lifestyle as well, information on healthy nutrition (product information, quantities, eating moments, eating locations) and how to help their children. Parents received advice on parenting styles (boundaries setting with regard to eating behavior, giving positive feedback). During the last meeting a therapist discusses the role of all other family members with regard to the treatment in the family (e.g. are other family members supportive, how do they cope with the lifestyle changes).
Follow-up meetings	In order to maintain the newly learned behavior refresh follow-up meetings were given during the first two years (2-3 meetings/ year). The child psychologist and the social worker organize this follow-up meetings. The topics repeated were: problem solving techniques and relapse prevention techniques.

The control group received standard care and advice, at start of the trial, on how to increase their physical activity, decrease their sedentary activities and improve their eating behavior according to Dutch standards for healthy nutrition. After 1 year all children in the control group were offered the opportunity to participate in the family-based multidisciplinary lifestyle intervention.

Clinical Measures

Measurements were taken before (T1) and after the 3 months treatment in the intervention group (T2) and after a follow-up period of 12 months after start (T3). The intervention group was also evaluated after 24 months (T4). In the normal weight control group tests and blood samples were determined once.

Weight was measured to the nearest of 0.1 kg using an electronic scale (SECA 911, Vogel & Halke, Hamburg, Germany) and height to the nearest of 0.1 cm with a stadiometer (Holtain, limited, Crymych, Dyfed, Britain) in underwear and barefoot by an experienced assistant. The BMI was calculated as weight / height squared (kg/m^2). Subjects were classified as obese using BMI gender- and age specific international cut-off levels (26). BMI was expressed as standard deviation score (SDS) for Dutch references (27). The 1980 reference data for weight and height were used to obtain a realistic view on the degree of obesity without data being biased by the increased prevalence rate of childhood obesity. Waist circumference (WC, in cm) was measured with an anthropometric tape midway between the lower rib margin and the iliac crest at the end of gentle expiration and expressed as SDS (WC-SDS) (28). The WC/height (both in cm) ratio (WC/Ht) was used as an additional measure for increased health risk. Blood pressure was determined in a relaxed sitting position measurement with an electronic device (Criton Dinamap, No. 8100), in duplicate; the last measurement was used for further analysis.

Ethnicity was determined according to self-reports by the parents. For this analysis subjects were classified as 'Northern European' (38% of the total sample) when both parents reported the Northern European ethnicity, and 'Others' (62%) when one or both parents reported another ethnicity. Subjects in the 'Others' group were mainly of Hindustani (28% of total sample) and Mediterranean (28% of total sample) origin.
Pubertal development was recorded by the pediatrician according to Tanner (29). Breast development in girls and genital development in boys was used for pubertal classification into two groups: prepubertal (breast or genital stage ≤1) and pubertal (stages 2-5).

Voluntarily Maximal Exercise Test

The physical fitness of the children was determined by a voluntary maximum exercise test on a treadmill using breath-by-breath analysis and plots according to Wasserman (30). The exercise test consisted of three stages; a reference stage (2 minutes rest prior to the exercise test), the test stage (the exercise test until voluntary exhaustion occurred) and a recovery stage (2 minutes recovery measurement in rest after the exercise test). The test stage started with a velocity of 4 km/h and an angle of 0% during 1 minute. Every minute the velocity increased with 0.5 km/h and the angle with 2%, until voluntary exhaustion occurred. During the test all subjects were verbally encouraged to perform maximally. At the end of the test the children were asked to grade the level of exhaustion using the Borg scale (31) and explain their reason to end the test.

Peak values were based on heart rate and a Respiratory Exchange Ratio (RER) of > 1.0 between oxygen uptake (VO_2) and carbohydrate output (VCO_2). This level is in children equivalent with the anaerobic threshold at which point exhaustion starts (32). This latter criterion is a generally accepted approach to establish if peak values are reached.
The physical fitness was determined from the absolute measured peak value of oxygen uptake (ml/min), standardized for age and gender (VO_{2peak}-SDS). Also the peak oxygen uptake adjusted for body weight was determined by dividing the absolute oxygen uptake by body weight (ml/min/kg) and standardized it for age and gender (VO_{2peak}-SDS-kg). In obese subjects it is common to use this latter approach for physical fitness because the peak value of the absolute oxygen uptake is biased since obese subjects usually also have a large absolute amount of muscle weight compared to normal weight peers (30).

Biochemical Measures

With the subject in a supine position, blood samples were taken by venipuncture after an overnight fast. Before blood sampling, the fasting state was verbally confirmed by the participant and the parent(s). After sampling blood, serum samples of insulin, adiponectin and hsCRP were stored at -80ºC before analysis. All blood samples were analyzed in accredited clinical chemical and hematology laboratories (HagaHospital, the Hague and Leiden University Medical Center, Leiden, The Netherlands)

Glucose was analyzed from lithium heparine plasma by the glucose-oxydase method with the Unicel DxC 800 (Beckman Coulter, Woerden, the Netherlands). Plasma insulin was analyzed by a RIA method (DSL-1600, Beckman Coulter, Woerden, the Netherlands; intra-assay coefficient of variation 4.5-8.3%; inter-assay coefficient of variation 4.7-12.2%; sensitivity 1.3µU/ml). An index for insulin resistance was calculated according to the Homeostasis Model Assessment for insulin resistance (HOMA-IR) formula: (fasting insulin (µU/mL) x fasting glucose (mmol/L)) / 22.5 (33). Standard deviation scores for HOMA-IR (HOMA-SDS) were calculated, based on gender- and age- specific reference values (34).
HDL cholesterol was analyzed by homogenic enzymatic colorimetry and triglyceride (TG) by automatized colorimetry, both determined by bynchon Lx20 Pro/ unicel DXC 800 (Beckman Couter, Brea, US).

High-sensitive CRP was analyzed by immune-turbidimetric assay with Cobas Integra 800 (Roche Diagnostics, Indianapolis, IN, USA; measuring range 0.15-20.0 mg/L; sensitivity 0.3 mg/L with an inter-assay coefficient of variation <10%). Adiponectin was assayed by human adiponectin RIA (adiponectin kit hadp-61hk, Millipore, Billerica, MA, USA; intra-assay coefficient of variation 1.78-6.21%; inter-assay coefficient of variation 6.9-9.25%; sensitivity; 0.78 ng/mL).

Statistical Analysis

The analysis was performed using the Statistical Package for Social Science version 17.0 for Windows (SPSS Inc., Chicago, IL, USA) and the level of significance was set at $p<0.05$. Data were checked for normality before analysis, using descriptive statistics for skewness, kurtosis and Shapiro-Wilk test. Fasting insulin was transformed to the natural logarithm. Data were expressed as mean ± standard deviation (continuous variables) and as count and percentage (categorical variables) unless defined otherwise. One-way ANOVA, with Bonferroni correction for multiple testing, was used to compare the intervention group, obese control group, and normal weight control group at baseline. ANOVA for repeated measures were used to determine the mean study parameters over time per group

(intervention and obese control group). The mixed model for repeated measures was used to determine the effect of intervention (mean difference between change in intervention and control group) over time for all the parameters separately, adjusted for baseline values. Pearson correlation analysis was used to assess the associations between the study parameters at baseline.

RESULTS

Clinical baseline data of 79 obese children (n=40 in the intervention group and n=39 controls) and of 34 normal weight children are shown in table 2. The ratio prepubertal (Tanner ≤ 1) vs. pubertal (Tanner 2-5) children was not significantly different between groups (p=0.11). At baseline the intervention and obese control group did not significantly differ in measures of adiposity (BMI-SDS, WC-SDS, WC/Ht), physical fitness (VO_{2peak}-SDS, VO_{2peak}-SDS-kg), metabolic parameters (insulin, glucose, HOMA-SDS, HDL, TG, blood pressure) and inflammation (adiponectin, hsCRP). At baseline the parents of both intervention and obese control group were on average obese as well, showing no significant difference between groups; BMI of the father (30.0 ± 7.1 kg/m^2 vs. 28.4 ± 4.4 kg/m^2, respectively) and BMI of the mother (31.0 ± 9.0 kg/m^2 vs. 31.2 ± 6.2 kg/m^2).

Table 2: *Baseline subject characteristics*

	Intervention group (n=40)	Control group (n=39)	Normal Weight Control group (n=34)
Gender (M/F)	18/22	19/20	14/20
Ethnicity (North European/Other)	14/26	11/28	18/16
Puberty (Tanner ≤1/ 2-5)	5/35	8/31	7/27
Age (yr.)	13.3 ± 2.0	13.1 ± 1.9	13.2 ± 2.4
Weight (kg)	85.7 ± 18.4*	85.7 ± 18.6*	51.7 ± 15.1
Height (cm)	161.9 ± 9.7	161.4 ± 11.0	160.2 ± 14.1
BMI (kg/m^2)	32.4 ± 4.7*	32.5 ± 3.9*	19.7 ± 3.3
BMI-SDS	4.2 ± 0.7*	4.3 ± 0.6*	0.5 ± 1.4
WC (cm)	91.1 ± 9.1*	90.5 ± 7.7*	67.0 ± 8.7
WC-SDS	3.7 ± 1.0*	3.7 ± 0.9*	0.3 ± 0.9
WC/Ht	0.56 ± 0.04*	0.56 ± 0.04*	0.42 ± 0.04
VO_{2peak}-SDS	1.7 ± 1.5*	2.2 ± 1.5*	0.0 ± 1.4
VO_{2peak}-SDS-kg	-3.0 ± 1.0*	-2.8 ± 1.0*	-0.8 ± 1.1
Glucose (mmol/L)	5.3 ± 0.4	5.2 ± 0.4	5.2 ± 0.5
Insulin (mU/L)	19.5 ± 12.2*	14.9 ± 8.0	13.5 ± 9.1
HOMA-IR	4.6 ± 2.9	3.4 ± 1.9	3.2 ± 2.3
HOMA-SDS	2.1 ± 2.3*	1.2 ± 1.3	1.0 ± 2.1
HDL (mmol/L)	1.1 ± 0.3*	1.1 ± 0.2*	1.3 ± 0.2
Triglycerides (mmol/L)	1.2 ± 1.0*	0.9 ± 0.5	0.7 ± 0.3
Systolic Blood Pressure (mmHg)	125 ± 13*	126 ± 12*	119 ± 9
Diastolic Blood Pressure (mmHg)	65 ± 9	65 ± 7	67 ± 9
Adiponectin (ng/mL)	8.6 ± 3.8	8.5 ± 3.3	9.7 ± 4.0
hsCRP (mg/L)	2.3 ± 2.1	1.8 ± 1.5	0.6 ± 0.9

Results are expressed as mean ± sd.

**significantly different compared to normal weight control group, p <0.05, tested using ANOVA for comparing between groups*

Obese subjects in both intervention and control groups showed a significantly ($p<0.01$) lower physical fitness (VO_{2peak}-SDS, VO_{2peak}-SDS-kg) and HDL compared to the normal weight control group and a higher systolic blood pressure (SBP) ($p=0.02$ and $p=0.06$, respectively). Significantly higher fasting insulin ($p=0.03$), HOMA-SDS ($p=0.05$) and TG ($p=0.01$) were found in the obese intervention group compared to the normal weight control group.

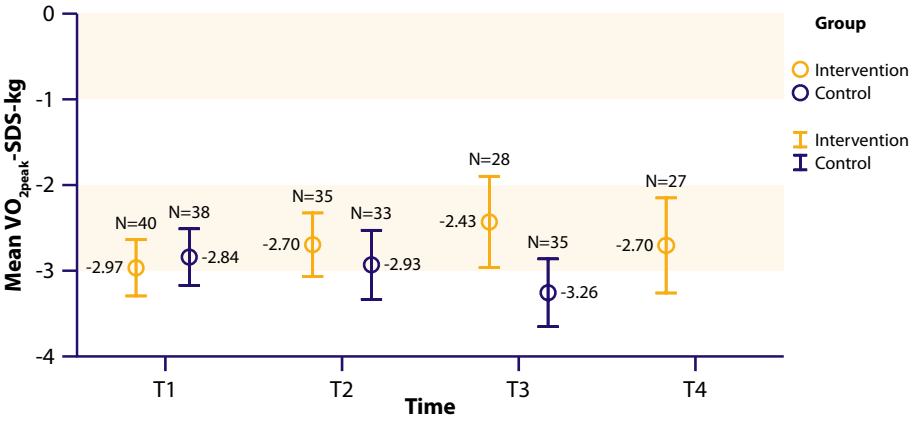
During the 3 months intensive phase of the treatment 5 boys and 5 girls missed 2 meetings, 2 boys and 5 girls missed one meeting, the remaining children attended all group meetings. The short-term (T2 at 3 months) and long-term (T3 after 1 yr follow-up) results are shown in table 3. On both these study occasions measures of adiposity were significantly reduced in the intervention group, with 10% decreased BMI-SDS and 19% decreased WC-SDS after 1 year follow-up compared to baseline. The corresponding values in the obese control group remained unchanged compared to baseline. After 1 year follow-up the VO_{2peak}-SDS-kg in the intervention group had increased by 20%, while a reduction of 18% was observed in the obese control group (Figure 2). Borg scores for subjective experienced exhaustion did not significantly change over time within and between groups. Measures for fasting insulin and HOMA-SDS were equal to baseline values in the intervention group at all study occasions. In the control group these measure slightly increased compared to baseline. Blood pressure decreased more in the intervention group versus baseline values compared to the obese control group. Lipid profile and inflammatory state in both groups remained unchanged.

Table 3: *Outcome parameters at start (T1), after 3 months (T2) and after 12 months (T3) in the intervention and control groups*

	Intervention group			Control group		
	T1 (n=40)	**T2 (n=36)**	**T3 (n=32)**	**T1 (n=39)**	**T2 (n=33)**	**T3 (n=35)**
BMI-SDS	4.2 [4.0;4.4]	4.0 [3.7;4.3]	3.8 [3.4;4.2]	4.3 [4.1;4.5]	4.2 [4.0;4.5]	4.2 [4.0;4.5]
WC-SDS	3.7 [3.3;4.0]	3.4 [2.9;3.8]	3.0 [2.5;3.6]	3.7 [3.4;4.0]	3.7 [3.3;4.1]	3.5 [3.1;4.0]
WC/Ht	0.56 [0.55;0.58]	0.55 [0.53;0.57]	0.53 [0.51;0.56]	0.56 [0.55;0.57]	0.56 [0.55;0.58]	0.56 [0.54;0.57]
VO_{2peak}-SDS	1.7 [1.2;2.2]	1.7 [1.2;2.2]	1.7 [1.1;2.3]	2.2 [1.7;2.7]	1.7 [1.2;2.2]	1.1 [0.6;1.6]
VO_{2peak}-SDS-kg	-3.0 [-3.3;-2.6]	-2.7 [-3.1;-2.3]	-2.4 [-3.0;-1.9]	-2.8 [-3.2;-2.5]	-2.9 [-3.3;-2.5]	-3.3 [-3.7;-2.9]
Glucose (mmol/L)	5.3 [5.1;5.4]	5.3 [5.1;5.4]	5.1 [5.0;5.2]	5.2 [5.1;5.3]	5.3 [5.0;5.6]	5.1 [5.0;5.3]
Insulin (mU/L)	19.5 [15.6;23.4]	17.4 [13.1;21.7]	20.5 [15.2;25.9]	14.9 [12.3;17.5]	20.3 [15.5;25.0]	18.8 [15.6;21.9]
HOMA-SDS	2.1 [1.4;2.9]	1.7 [0.8;2.5]	2.2 [1.1;3.3]	1.2 [0.7;1.6]	2.2 [1.1;3.4]	1.7 [1.2;2.3]
HDL (mmol/L)	1.1 [1.1;1.2]	1.1 [1.0;1.2]	1.1 [1.0;1.2]	1.1 [1.1;1.2	1.2 [1.0;1.3]	1.1 [1.0;1.2]
TG (mmol/L)	1.2 [0.8;1.5]	1.2 [0.9;1.5]	1.1 [0.8;1.4]	0.9 [0.8;1.1]	1.0 [0.9;1.2]	1.0 [0.8;1.3]
SBP (mmHg)	125 [121;129]	123 [119;127]	118 [114;122]	126 [123;131]	125 [121;129]	122 [177;128]
DBP (mmHg)	65 [62;67]	59 [56;62]	57 [54;61]	65 [62;67]	62 [58;66]	59 [56;62]
Adiponectin (ng/mL)	8.6 [7.4;9.8]	9.2 [7.5;10.9]	9.4 [7.4;11.4]	8.5 [7.4;9.6]	9.1 [7.8;10.5]	8.9 [7.3;10.5]
hsCRP (mg/L)	2.3 [1.6;3.0]	1.9 [1.2;2.6]	1.9 [1.1;2.8]	1.8 [1.3;2.3]	2.5 [1.4;3.7]	2.1 [1.5;2.8]

Results are expressed as mean [95% CI].

Figure 2: *Physical fitness over time in Intervention and Control group*



Error bars: 95% CI

The effect of the intervention on the outcome parameters after 1 year follow-up is shown in table 4 as well. In order to adjust for differences in baseline values between groups, the baseline values were put in the model as covariates. The mean differences between the intervention and obese control group, adjusted for baseline differences, were statistically significant for all the parameters of adiposity (BMI-SDS, WC-SDS, WC/Ht), physical fitness (VO_{2peak}-SDS, VO_{2peak}-SDS-kg) and for HOMA-SDS.

Table 4: *Effect of intervention on markers of adiposity, physical fitness, metabolic parameters and inflammation*

Parameters	Intervention group		Obese control group		Difference between two obese groups	
	Change during first 12 months	95% CI	Change during first 12 months	95% CI	Mean difference adjusted for baseline [95% CI]	p-value
BMI-SDS	-0.4	-0.8; 0.0	-0.1	-0.4; 0.3	-0.2 [0.03;0.42]	0.02
WC-SDS	-0.6	-1.2; -0.0	-0.2	-0.7; 0.5	-0.4 [0.04;0.78]	0.03
WC/Ht	-0.03	-0.06; 0.0	-0.01	-0.03; 0.0	-0.02 [0.001;0.034]	0.03
VO_{2peak}-SDS	0.0	-0.7; 0.8	-1.1	-1.8;-0.4	0.7 [-1.1;-0.3]	<0.01
VO_{2peak}-SDS-kg	0.5	-0.0; 1.1	-0.4	-0.9; 0.1	-0.7 [-1.1;-0.4]	<0.01
Glucose (mmol/L)	-0.2	-0.3; 0.0	-0.0	[-0.3; 0.2]	0.1 [-0.1;0.3]	NS
Insulin (mU/L)	1.0	-7.2; 5.2	3.9	-1.1; 8.9	-4.0 [-0.0;8.0]	0.05
HOMA-SDS	0.1	-1.1; 1.1	0.6	-0.5;1.6	-0.9 [0.0;1.7]	0.04
HDL (mmol/L)	-0.0	-0.2; 0.1	-0.0	-0.2;0.1	-0.03 [-0.11;0.06]	NS
Triglycerides (mmol/L)	-0.1	-0.5; 0.4	0.1	-0.2; 0.4	-0.04 [-0.3;0.2]	NS
SBP (mmHg)	-6.6	-12.2; -1.0	-4.3	-10.2; 1.7	-2.8 [-7.0;1.5]	NS
DBP (mmHg)	-7.3	-11.5;-3.1	-5.7	-10.0; -1.3	-3.2 [-6.7;0.4]	NS
Adiponectin (ng/mL)	0.8	-1.5; 3.0	0.4	-1.4; 2.3	0.2 [-0.9;1.4]	NS
hsCRP (mg/L)	-0.4	-1.4; 0.6	-0.9	-3.2; 1.4	-0.8 [-1.6;0.1]	NS

At 2-year follow-up, data on adiposity and physical fitness were available in 31 children in the intervention group. Measures for adiposity were similar to T3 (3.8 ± 1.2 BMI-SDS and 3.2 ± 1.8 WC-SDS). BMI-SDS was still significantly lower than at baseline in these 31 children (4.2 ± 0.7 SDS, p=0.02) but only 3 children reached a BMI < +2 SDS. The physical fitness adjusted for body weight was still 10% better compared to baseline, but had returned to the T2 value (-2.7 ± 1.4mL/min/kg).

Pearson correlation analyses between the study parameters at baseline are shown in table 5. A strongly significant inverse correlation was found between adiposity (BMI-SDS, WC-SDS, WC/Ht) and VO_{2peak}-SDS-kg. A less pronounced positive relation was found for all markers for adiposity with metabolic parameters (fasting insulin, HOMA-SDS, TG, SBP) and hsCRP and an inverse relationship with HDL and adiponectin. Physical fitness, adjusted for body weight, correlated inversely with metabolic parameters (fasting insulin, fasting glucose, HOMA-SDS, TG, SBP) and with hsCRP, and correlated positively with HDL and adiponectin. An inverse correlation was found between adiponectin and HOMA-SDS and SBP. A positive correlation was found between adiponectin and HDL.

Table 5: *Pearson correlation Coefficients of the study parameters at baseline*

	BMI-SDS	WC-SDS	WC/Ht	VO_{2peak}-SDS	VO_{2peak}-SDS-kg	Fasting Glucose	Fasting Insulin	HOMA-SDS	HDL	TG	SBP	DBP	Adiponectin	hsCRP
BMI-SDS	-													
WC-SDS	.903**	-												
WC/Ht	.899**	.962**	-											
VO_{2peak}-SDS	.549**	.620**	.487**	-										
VO_{2peak}-SDS-kg	-.707**	-.737**	-.755**	-.061	-									
Fasting Glucose	.032	.042	.091	-.158	-.186*	-								
Fasting Insulin	.330**	.331**	.298*	.040	-.354**	.304**	-							
HOMA-SDS	.189**	.217*	.239*	-.017	-.356**	.457**	.433**	-						
HDL	-.459**	-.466**	-.429**	-.326**	.319**	-.048	-.223*	-.243**	-					
TG	.258**	.282**	.249**	.139	-.218*	.047	.366**	.125	-.370**	-				
SBP	.306**	.398**	.379**	.173	-.381*	.056	.163	.213*	-.286**	.202*	-			
DBP	-.010	.054	.058	.012	-.018	-.008	.049	.079	-.097	.114	.269**	-		
Adiponectin	-.260**	-.272**	-.240*	-.118	.250**	-.049	-.391**	-.297**	.323**	-.110	-.220*	.001	-	
hsCRP	.221*	-.189*	.242**	.070	-520**	.106	-.008	-.036	-.197*	-.056	.043	.109	-.089	-

** correlation is significant at the 0.05 level (2-tailed);*

*** correlation is significant at the 0.01 level (2-tailed)*

DISCUSSION

Our family-based multidisciplinary lifestyle intervention showed a positive effect on all parameters of adiposity and physical fitness directly after the intervention and at follow up after 1 and 2 years. We also found a modest but significant intervention effect on insulin resistance (expressed as HOMA-SDS), i.e. unchanged values over time in the intervention group compared to increasing values of HOMA-SDS with persisting adiposity in the obese control group. Results for parameters of lipid profile and inflammation showed no significant treatment effect.

The current recommendation for treating childhood obesity is a multidisciplinary lifestyle intervention with parental involvement. However, only few programs have been evaluated and the effect on retaining weight reduction over time is small to moderate (14;16;35). These previous observations are confirmed by our study, showing a positive short- and long-term intervention effect on adiposity and physical fitness. Concerning the short-term treatment effect on adiposity, our results are similar to those of numerous previous studies on multidisciplinary lifestyle interventions in obese children (16;20;21;24). The follow-up results of such interventions are more diverse. While, in agreement with our findings, some investigators observed still a reduced BMI-SDS after ≥ 1 year follow-up (14;18), others reported less favorable follow-up results (14;21). Nevertheless, on average the children were still obese during these follow-up measures. However, even if such interventions cannot reduce body weight to the normal range, beneficial results on health can be accomplished by improving physical fitness, nutritional habits and coping strategies (14;35).

Waist circumference is used as a safe, easy and inexpensive way to measure abdominal obesity in adults and children, and is considered a good indicator of increased metabolic and cardiovascular risk (36). According to a previous study obese children only had an increased metabolic and cardiovascular risk compared to normal weight children if WC was >90th percentile for age and gender (36). In addition, among Asian Indian adolescents the odds of having hypertension was more pronounced for increased WC (5.21; 95% CI [2.14 to 12.17]) than for increased BMI (2.90; 95% CI [1.40 to 6.12]) (37). These findings suggest that during treatment not only a reduction of BMI-SDS but also a lower WC is important to establish a beneficial health effect. In this light our observations of a significant positive treatment effect on WC-SDS over time suggests to be of greater importance for improvement of metabolic risk than the reduction of BMI-SDS.

The beneficial effect of multidisciplinary lifestyle interventions has been shown to increase when parents are in some way involved in the intervention (35). So, in order to achieve a larger treatment effect more emphasis should be put on motivating the parents to participate and support their child. The inclusion of the parents in the treatment of childhood obesity is challenging and health professionals are often confronted with the lack of parental motivation and with time constraints of the parents. A further obstacle in the struggle against childhood obesity is the unrealistic treatment expectations of children and parents. In most studies, including the current one, children who participate in a multidisciplinary lifestyle intervention do not lose all their excess body weight, which most families find difficult to accept. In order to match expectations with treatment objectives, it is advised to include an interview with the child and parents prior to the program. The purpose of this interview is to give the family a chance to reflect their willingness to participate, and discuss achievable realistic treatment goals. Although we included such an interview in our program, the child and parents kept focusing on the

absolute amount of body weight loss and found it difficult to maintain the newly learned lifestyle. Therefore, the period immediately after the family-based multidisciplinary lifestyle intervention is critical for motivating children and their parents to maintain their changed lifestyle. In this respect, it may be important to emphasize the favorable effects of the achieved results in terms of body proportions and metabolic parameters, rather than the modest weight reduction obtained by the large majority.

Besides the treatment effect on adiposity, we also found a significant effect on physical fitness. Our data showed a significant improvement of fitness over time as opposed to a significant deterioration of physical fitness when BMI-SDS was unchanged as seen in the untreated controls. It has been suggested that the measured absolute peak oxygen uptake in obese subjects may overestimate the real physical fitness because of their increased body size (30). For that reason the peak oxygen uptake adjusted for body weight, age and gender (VO_{2peak}-SDS-kg) is often determined to establish a more realistic value for the physical fitness. In line with earlier studies (20;38), we found in our intervention group unchanged absolute physical fitness (VO_{2peak}-SDS) over time, while physical fitness adjusted for body weight improved. It appears that absolute fitness is unaffected by treatment, but both measures for physical fitness diminished over time in our obese control group. A stable absolute physical fitness over time has been suggested to be indicative of training adaptation (38). As peak oxygen consumption is directly related to fat free mass (30) and subjects' fat mass as well as their fat-free mass often decrease during weight reduction, their absolute physical fitness is expected to be lower at the end of treatment. An obstacle in maintaining prolonged weight reduction is, however, that during weight loss not only body weight decreases, but as a consequence of the reduced body weight, also the average daily energy requirements. For prolonged weight reduction it will be beneficial to increase physical fitness in order to prevent loss of fat free mass during the weight loss period. Since we did not measure the fat free mass in our study, we were unable to determine a possible positive training adaption.

The intervention did not improve insulin resistance, but still a treatment effect was observed because of the increased insulin resistance in the control group. In contrast to our results, prior studies have found a significantly decreased HOMA-IR and fasting insulin after a lifestyle intervention. These decreased markers for insulin resistance were found when clinically significant weight reduction (>0.5 BMI-SDS) occurred (22), or when BMI and body weight were significantly reduced (19). It should, however, be noted that the result of the latter study was found in only 48 of the 104 children (47.5%) after completion of the intervention. Therefore, it is conceivable that, in this study, markers for insulin resistance were determined only in the children with weight reduction.

The results of the present study confirm the previously reported association between childhood obesity and the presence of a pro-inflammatory state, indicated by a significantly increased hsCRP serum concentration (7-9). On the contrary, adiponectin exerts an anti-atherogenic and has previously been found in lower concentrations in obese compared to normal weight children (10;19;22). Adiponectin is also reported to improve insulin sensitivity (39). In contrast to these earlier studies, we found similar adiponectin concentrations in the obese and lean children. A beneficial effect of our family-based multidisciplinary lifestyle intervention on the inflammatory state was absent. In earlier studies, a clinically significant BMI-SDS reduction of > 0.5 has been (9;22) associated with a significant increase in adiponectin and decrease in hsCRP. We speculate that the modest BMI-SDS reduction after intervention may explain the absence of a treatment effect on both.

One of the limitations of this study is that our study population consisted of a clinically referred sample and thereby may be influenced by selection and referral bias, and thus may not be representative for all (severely) obese children in the general population. Treatment seeking children with obesity probably experience more disadvantages from their excess body weight and are therefore perhaps more motivated than their obese peers in the community. Another limitation of the current study is that for the follow-up at 2 years no obese control data were available, since, for ethical reasons, the obese control group was offered the same intervention at 1-year follow-up. Finally, it is unknown what the predictive value is of two year follow-up data for health and behavior in later years. The strength of this study is the prospective, randomized and controlled study design, with sufficient statistical power, and the breadth of outcome parameters, including physical fitness. Since at all points in time during our study measurements were taken by the same person under similar conditions, the results cannot be biased by inter-observer errors.

In conclusion, our intensive family-based multidisciplinary lifestyle intervention resulted in a modest long-term reduction of both total and abdominal adiposity accompanied by improved physical fitness, while unchanged adiposity in untreated controls led to decreased physical fitness and deterioration of insulin resistance state. No effect was seen on inflammatory markers, probably because almost all children remained obese.

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CONFLICT OF INTEREST STATEMENT

The study was partly funded by an unrestricted educational grant by Pfizer and an unrestricted educational grant by a non-profit foundation (de Stichting Vrienden van het JKZ). The sponsors had no role in the study design, data collection and analysis, nor the content of the manuscript. The corresponding author has full access to all data in the study. All authors declare no conflict of interest. This research was carried out at the Department of Pediatrics, Juliana Children's Hospital, The Hague, the Netherlands.

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Chapter 4

The Effect of Multidisciplinary Lifestyle Intervention on the Pre- and Postprandial Plasma Gut Peptide Concentrations in Children with Obesity

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Submitted

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4 The Effect of Multidisciplinary Lifestyle Intervention on the Pre- and Postprandial Plasma Gut Peptide Concentrations in Children with Obesity

ABSTRACT

Objective
This study aims to evaluate the effect of multidisciplinary treatment of obesity on plasma concentrations of several gut hormones in fasting condition and in response to a mixed meal in children.

Methods
Complete data were available from 36 obese children (age 13.3±2.0yr). At baseline and after the 3-months multidisciplinary treatment, fasting and postprandial blood samples were taken for glucose, insulin, ghrelin, peptide YY (PYY) and glucagon like peptide 1 (GLP-1).

Results
BMI-SDS was significantly reduced by multidisciplinary treatment (from 4.2±0.7 to 4.0±0.9, $p<0.01$). The intervention significantly increased the area under the curve (AUC) of ghrelin (from 92.3±18.3 to 97.9±18.2 pg/L, $p<0.01$), but no significant changes were found for PYY or GLP-1 concentrations (in fasting or postprandial condition). The insulin resistance index (HOMA-IR) remained unchanged as well.

Conclusion
Intensive multidisciplinary treatment induced moderate weight loss and increased ghrelin secretion, but serum PYY and GLP-1 concentrations and insulin sensitivity remained unchanged.

Trial Registration
http://www.controlled-trials.com/ISRCTN36146436.

Keywords: obesity, children, ghrelin, PYY, GLP-1

4 The Effect of Multidisciplinary Lifestyle Intervention on the Pre- and Postprandial Plasma Gut Peptide Concentrations in Children with Obesity

INTRODUCTION

Childhood obesity has become a global problem (1). Understanding the mechanisms that control energy balance and fuel flux in children is of paramount importance for the design of effective strategies to combat this health hazard. The gastrointestinal tract plays a critical role in the control of feeding behavior and fuel metabolism. In response to food intake, the gut produces a variety of hormones that inhibit food intake, promote glucose induced insulin release and/or facilitate insulin action (e.g. glucagon-like peptide 1 (GLP-1), peptide YY (PYY)) (2-4). Conversely, in the absence of food, the stomach produces ghrelin, which stimulates appetite to initiate feeding (4;5).

In a number of studies plasma levels of ghrelin in obese children were compared with those of normal weight controls. Generally, the plasma ghrelin concentration of obese children is lower in fasting condition (6-10), whereas the decline in response to glucose ingestion varies as a function of insulin sensitivity; the decline appears to be less profound in insulin resistant obese children (6;11), although the data are equivocal (12). Weight loss tends to normalize circulating ghrelin levels (8;10;13), although this is still subject for debate (5;14).

In fasting condition, plasma GLP-1 and PYY levels were reported to be similar in obese and lean children (9;15-18), but in other studies lower PYY (19) and lower GLP-1 were found in obese children (20). Postprandial concentrations of the two hormones are consistently lower in obese vs. normal weight peers (15;20;21). The few studies that have examined the effect of weight loss on the release of these hormones in obese children found significantly increased fasting PYY (19) and (surprisingly) decreased fasting GLP-1 (18) after weight reduction.

Because gut hormones are intimately involved in the control of energy balance, better understanding of intestinal endocrine (mal)function in obese children may contribute to the development of strategies to treat their condition. Here we aim to evaluate the effect of a 3 months' multidisciplinary intervention program to reduce the bodyweight of obese children on plasma gut hormone concentrations in fasting condition and in response to a standard meal.

MATERIALS AND METHODS

Participants, Study design and Settings

This study is part of a randomized clinical trial on the effect of multidisciplinary treatment on childhood obesity (22). Here the effects of lifestyle intervention on various clinical and physiological features of the obese children in the intervention group are analyzed. The study inclusion criteria were simple obesity (as defined by Cole (23)), age 8-17 years and referral to a pediatrician. Potential participants were excluded if their knowledge of the Dutch language, intelligence or social skills were insufficient to participate in the trial. Other exclusion criteria were use of medication that might have an effect on weight loss, medical co-morbidity (e.g. hypothyroidism, high dose of glucocorticoids, diabetes mellitus) that could affect trial outcome or previous enrollment in another cognitive behavioral treatment program with a focus on reducing body weight. Forty-one children were randomized to the intervention group, of whom 36 completed the treatment. The study was conducted according to the 'Declaration of Helsinki', and approval was obtained from the regional medical ethical committee South West Holland. All parents and children gave their written informed consent after they had been given detailed written explanations of the aims of the study, discomfort, and inconvenience, and the option to withdraw at any time.

Intervention

The multidisciplinary lifestyle treatment of the intervention group consisted of a screening phase of individual counseling of the children with their parents, followed by an intensive phase of group sessions during three months. The group treatment consisted of 7 group meetings for the children, 5 separate parent meetings and 1 parent meeting together with the children. Meetings of 2.5 hours were held once every 2 weeks. The children meetings were held on weekday afternoons at the hospital. The 5 separate parent meetings were provided on weekdays after working hours. Subsequently, refresh follow-up sessions (2-3 sessions/year) were offered for a total period of two years (Table 1).

Table 1: *Characteristics of the Family-based multidisciplinary lifestyle intervention*

Components	Description
Screening phase/ individual counseling	During the screening phase, children and their parents were interviewed at two separate occasions and all individually by the multidisciplinary team consisting of a dietitian, a child-physiotherapist, a child-psychologist and a social worker. Throughout those two separate meetings, an individual advice was given by the multidisciplinary team, based on the personal situation of each participating family.
Individual nutritional advice	A 3-day dietary recall (1 weekend day included) was used by the dietitian to get more insight in dietary habits of the children. Information was provided about nutrition and healthy eating behavior according to the traffic light nutritional list (28). The traffic light nutritional list identifies several main food groups (fruits, vegetables, grains, milk and other dairy products, meat, fish, and others). Foods within each group were color-coded so as to reflect the caloric density per average serving and Dutch standards for healthy nutrition. The colors are green for "go", orange for "approach with caution", and red for "stop". The children and parents were involved in planning their own daily diet for themselves according to the traffic light nutritional list.
Individual physical activity counseling	To obtain insight in the child's general physical activity behavior during the week, a physical activity questionnaire was filled out by a child physiotherapist. Children were asked how they traveled to school (by foot, by bicycle, by public transportation or by car), physical fitness classes at school, spire time sport activities and daily computer and TV use as well as the duration spend at all these activities. The information from this questionnaire was used for advice on how to increase and optimize physical activity during everyday life, such as walking to nearby destinations and reducing sedentary activities (computer and TV use).
Individual psychological counseling	By means of motivational interviewing the child psychologist helped the children to adapting to a new lifestyle in order to reduce body weight. Before the child started with the group sessions individual treatment goals (reduction of 10% of body weight during 3 months group sessions) were written down in a contract to avoid disappointment.
Children's group meetings	Most children with obesity have negative experiences with group activities. For example, they are often not included in social events or chosen last by peer during sport activities. Therefore, during the first session much time is spent in getting acquainted with each other. A good group bond is important for the effect of the treatment because peer support can be very helpful in the treatment of obese children. The main educational focus of the first two meetings is on nutritional information of a healthy eating pattern and the balance between energy intake and energy expenditure. During the subsequent meetings, emphasis was put in self-control techniques to cope with difficult situations (e.g. birthday parties, holidays, lunch breaks at school, being at home alone). Problem solving alternatives are debated (e.g. to avoid a situation, doing something else, participate in a situation and eat less, or participate followed by extra exercise afterwards). Other psycho-educational topics reviewed were self-reward (when coping well with a difficult situation) and self-regulation situations (making a plan how to integrate healthy behavior in daily living). Stimulus control was also one of the psycho-educational topics (remove unhealthy stimuli at home, encourage healthy behavior, eat at the dinner table, reduction of environmental stimuli linked to eating). Topics of the last two meetings were self-image (focus on positive things about themselves) and coping strategies on dealing with teasing.
Parent group meetings	Topics discussed during the parent meetings included the necessity to change their own lifestyle as well, information on healthy nutrition (product information, quantities, eating moments, eating locations) and how to help their children. Parents received advice on parenting styles (boundaries setting with regard to eating behavior, giving positive feedback). During the last meeting a therapist discusses the role of all other family members with regard to the treatment in the family (e.g. are other family members supportive, how do they cope with the lifestyle changes).
Follow-up meetings	In order to maintain the newly learned behavior refresh follow-up meetings were given during the first two years (2-3 meetings/ year). The child psychologist and the social worker organize this follow-up meetings. The topics repeated were: problem solving techniques and relapse prevention techniques.

Clinical Measures

In this paper the measurements taken at baseline (T1) and after 3 months treatment (T2) are analyzed and discussed. Weight was measured to the nearest of 0.1 kg using an electronic scale (SECA 911, Vogel & Halke, Hamburg, Germany) and height to the nearest of 0.1 cm with a stadiometer (Holtain, limited, Crymych, Dyfed, Britain) in underwear and barefoot by an experienced assistant. The BMI was calculated as weight / height squared (kg/m^2). Subjects were classified as obese using BMI gender- and age specific international cut-off levels (23). BMI was expressed as standard deviation score (SDS) for Dutch references using the LMS method (24). Pubertal development was recorded by the pediatrician according to Tanner (25).

Mixed meal tolerance test

The children were asked to consume a daily amount of at least 150g carbohydrates three days prior to the mixed meal tolerance test and to continue their normal daily physical activities. The day before the test the subjects were asked not to consume any food or drinks after 10 pm, with the exception of tap water. On the morning of the mixed meal tolerance test the fasting state was verbally confirmed by the participant and a parent. A catheter was placed in an antecubital vein for blood sampling. Fasting blood samples were taken twice with a 15 minutes interval (t=-15 and t=0). After the second fasting blood sample was taken, the participants received a mixed meal bolus of 200mL (Nutridrink Yoghurt Style, Nutricia, Zoetermeer, The Netherlands). The mixed meal bolus consisted of 49% carbohydrates, 35% lipids and 16% proteins, with a total caloric content of 300 kcal. After the consumption of the mixed meal bolus, blood samples were taken two more times with a 15 minutes interval (t=15 and t=30) and four times with 30 minutes intervals (t=60, t=90, t=120 and t=150). Blood samples were analyzed for total ghrelin, PYY, GLP-1, glucose and insulin.

Laboratory analysis

Tubes for blood collection of GLP-1, PYY and ghrelin and the inhibitor dipeptidyl peptidase IV (DPP-IV) (Linco Research, St. Charles, MO, USA) were placed on ice. Immediately after blood sampling, DPP-IV was added to tubes for measurement of GLP-1 and PYY to prevent degradation of these hormones. Blood samples for GLP-1, PYY and ghrelin were centrifuged within one hour after sampling and stored at -80^{o}C until analyzed. Baseline and T2 samples were analyzed in the same batches for all three hormones. Serum GLP-1 concentrations were measured by a highly-specific enzyme-linked immunosorbent assay (human active GLP-1 ELISA Kit EGLP-35K, Linco Research, St. Charles, MO, USA; intra-assay coefficient of variation 8 ± 4.8%; inter-assay coefficient of variation 7.4 ± 1.1%; sensitivity 2pM/L). PYY(3-36) concentration was determined by human radioimmunoassay (RIA) (PYY-67HK RIA Kit A 0.056, LincoResearch, St. Charles, MO, USA; intra-assay coefficient of variation 5.5-8.5%; inter-assay coefficient of variation 2.9-9.4%; accuracy 86.9± 5.2%). Total serum ghrelin was determined by human RIA as well (Ghrelin Total RIA GHRT-89HK Kit A 0.056 MBQ, Linco Research, St. Charles, MO, USA; intra-assay coefficient of variation 0.9-1.3%; inter-assay coefficient of variation 6.2-7.8%; sensitivity 30 pg/mL).
Glucose was analyzed from lithium heparine plasma by the glucose-oxydase method with the Unicel DxC 800 (Beckman Coulter, Woerden, the Netherlands). Plasma insulin concentration was measured by RIA (DSL-1600, Beckman Coulter, Woerden, the Netherlands; intra-assay coefficient of variation 4.5-8.3%; inter-assay coefficient of variation 4.7-12.2%; sensitivity 1.3µU/mL). An index for insulin resistance was calculated according to the Homeostasis Assessment Model for insulin resistance (HOMA-IR) formula: (fasting insulin (µU/mL) x fasting glucose (mmol/L)) / 22.5 (26).

Statistical analysis

The analysis was performed using the Statistical Package for Social Science SPSS, version 17.0 for Windows (SPSS Inc., Chicago, IL, USA) and the level of significance was set at $p<0.05$. Data were checked for normality before analysis, using descriptive statistics for skewness, kurtosis and Shapiro-Wilk test. The outcome variables for insulin were transformed to the natural logarithm. Data were expressed as mean ± standard deviation (continuous variables) and as count and percentage (categorical variables) unless otherwise defined. Values for the area under the curve (AUC) of 165 min (from t=-15 to t=150 min) were calculated according to the trapezoid rule.
Paired t-tests were used to explore difference of the outcome variables after treatment, in total 16 paired t-tests were performed. A separate ANCOVA analysis was performed to determine if the change in AUC of the gut hormones over time (T2 vs. T1) was effected by gender, age, pubertal stage or change in BMI-SDS. In the ANCOVA analysis the changes in AUC of the gut hormones were used as dependent variables, time (T2 vs. T1) and gender as fixed variables and age, pubertal stage and change in BMI-SDS as covariates.

RESULTS

Subjects

Forty-one subjects (18M/22F; age: 13.3 ± 2.0 years) were enrolled in the study, and 36 children completed both study occasions. One subject withdrew before all baseline measurements were completed, two discontinued treatment and two did not show up at T2 for personal reasons. No significant difference in baseline BMI-SDS or age was observed between completers (4.2 ± 0.7 SDS; 13.3 ± 1.8 years) and noncompleters (4.3 ± 0.3; 13.3 ± 3.1 years). Results are presented for the 36 children completing both study occasions (18M/18F).

Anthropometry and Metabolic parameters

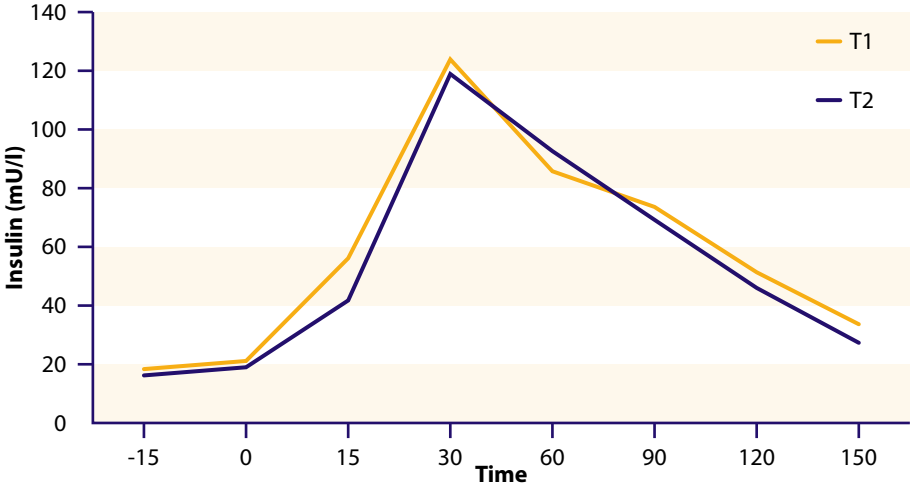
Changes between both study occasions in anthropometry and metabolic parameters are shown in table 2. A significant reduction of BMI-SDS was found after 3 months multidisciplinary lifestyle treatment.
Fasting plasma glucose and insulin concentrations (and consequently HOMA-IR) were similar at baseline (T1) and after treatment (T2). The AUC of plasma glucose and insulin concentrations in response to the meal was also not affected by intervention (Figure 1).

Table 2: *Clinical and physiological parameters of the subjects with complete data (N=36)*

VARIABLES	BASELINE (T1)	AFTER (T2)	P-VALUE*
BMI-SDS	4.2 ± 0.7	4.0 ± 0.9	0.003
HOMA-IR	4.2 ± 2.5	4.1 ± 3.0	NS
Glucose (fasting) (mmol/L)	5.2 ± 0.4	5.3 ± 0.4	NS
Glucose AUC (165 min × mmol/L)	905 ± 67	896 ± 86	NS
Insulin (fasting) (mU/L)	18.0 ± 10.7	17.4 ± 12.5	NS
Insulin AUC (165 min × U/L)†	10.3 ± 6.1	11.0 ± 8.0	NS
Ghrelin (fasting) (pg/mL)	612 ± 143	641 ± 144	NS
Ghrelin AUC (165 min × pg/L)†	92.3 ± 18.3	97.9 ± 18.2	0.006
PYY (fasting) (pg/mL)	90.2 ± 34.6	95.5 ± 32.8	NS
PYY AUC (165 min × pg/L)	16.3 ± 4.6	15.3 ± 5.0	NS
GLP-1 (fasting) (pM/L)	2.6 ± 0.9	2.5 ± 0.9	NS
GLP-1 AUC (165 min × pM/L)	567 ± 192	552 ± 197	NS

** p-value T2 vs. T1 (paired t-test)*

Figure 1: *Plasma levels of insulin in response to a mixed meal at baseline (T1) vs. after intervention (T2)*



Gut hormones

The ghrelin AUC in response to the meal were slightly, but significantly increased after treatment. Fasting levels were not significantly affected (Figure 2). The treatment did not affect either fasting or postprandial plasma GLP-1 and PYY concentrations (Figures 3 and 4).

The ANCOVA analysis for change of circulating ghrelin and PYY levels between the two study occasions showed that the change in BMI-SDS during the study period was a significant covariate ($p<0.01$ and $p=0.01$ respectively). This finding suggests that weight loss affects the plasma PYY concentration. Gender, age and pubertal stage were no significant covariates.

Figure 2: *Plasma levels of ghrelin in response to a mixed meal at baseline (T1) vs. after intervention (T2)*

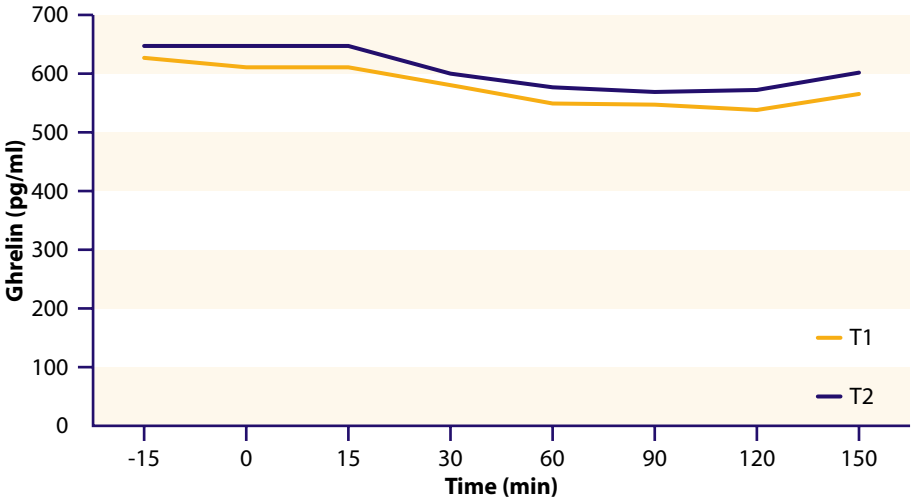


Figure 3: *Plasma levels of GLP-1 in response to a mixed meal at baseline (T1) vs. after intervention (T2)*

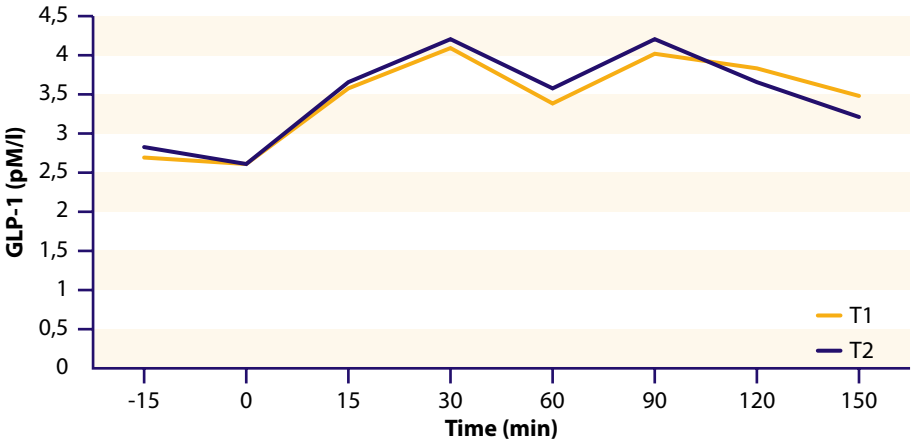
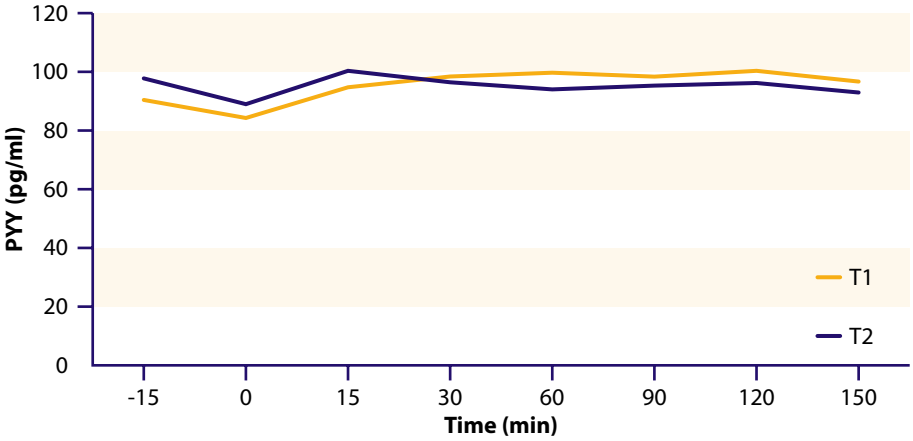


Figure 4: *Plasma levels of PYY in response to a mixed meal at baseline (T1) vs. after intervention (T2)*



DISCUSSION

A 3 months multidisciplinary lifestyle intervention in obese children reduces adiposity (BMI-SDS) and elevates plasma ghrelin levels in response to a meal. In contrast, it does not affect circulating PYY and GLP-1 concentrations in fasting condition nor in response to food intake. Notably, changes of ghrelin and PYY AUC were significantly influenced by the change of BMI-SDS, which suggests that the production of these gut peptides is sensitive to body weight (change). We speculate that the impact of our intervention on BMI was too modest to reach statistical significance for the difference between average levels.

Various studies have shown an increase of fasting plasma ghrelin levels after weight loss in obese children (8;10;13). However, the amount of weight lost was substantially greater in these studies than in ours. Other studies in which weight loss was more modest did not observe significant changes of fasting circulating ghrelin levels either (5;14). Interestingly, the change of plasma ghrelin concentrations was significantly and inversely associated with the change of BMI-SDS, which confirms that body weight (or caloric restriction) does influence ghrelin levels. This suggests that the effect of our intervention on weight reduction was too small to affect average fasting circulating ghrelin.
It has been suggested that weight loss achieved by dietary or exercise treatment initiates compensatory changes in appetite and energy expenditure that hinders maintenance of the reduced body weight (4;5). Ghrelin release increases before a meal to initiate food intake (4;27). Thus, it is conceivable that higher (fasting) ghrelin concentrations in response to weight loss set off a greater hunger signal, which obviously renders the treatment goal more difficult to reach.

It is unclear why serum ghrelin levels are low in obese children. Perhaps overfeeding is involved (feeding dampens ghrelin release) and the metabolic changes associated with obesity, such as insulin resistance (4). Indeed, a previous study revealed that the change of HOMA-IR after weight loss correlates inversely with the change in plasma ghrelin in obese children, suggesting that these changes are mechanistically linked (5;8).

GLP-1 and PYY are gut peptides produced in response to food intake. Both peptides provide a satiety signal to the brain to terminate eating (4). Fasting plasma concentrations of either peptide were reported to be normal (9;15-18) or reduced (19;20) in obese children, whereas postprandial levels are consistently lower (15;20;21). We show that modest weight reduction does not have an impact on fasting or postprandial GLP-1 and PYY levels in obese children. This is in apparent contrast to the results of the very few previous studies evaluating the effect of weight loss on plasma gut hormone levels in children. Substantial weight loss (≥0.5 BMI-SDS) appears to be accompanied by an increase in fasting PYY (19) and (surprisingly) a decrease in (fasting) GLP-1 (15;18).

It is important to emphasize that our multidisciplinary lifestyle treatment resulted in a statistically significant but only modest weight reduction. It is therefore conceivable that a more substantial average weight reduction of ≥ 0.5 BMI-SDS would have had more explicit effects on (average) gut hormone concentrations. This postulate is supported by other studies, but also by our own data showing that the amount of weight loss is correlated with counterregulatory changes of plasma ghrelin and PYY concentrations, which can contribute to the difficulties that patients encounter when they try to lose weight. Thus, GLP-1 analogues or dipeptidyl-peptidase IV inhibitors may help obese children to lose weight in response to lifestyle measures.

In conclusion, only a few studies so far have evaluated the effect of weight reduction on (postprandial) PYY, GLP-1 or ghrelin concentrations in children with obesity. We show that modest weight reduction by lifestyle intervention slightly elevates ghrelin levels, whereas it does not affect PYY or GLP-1 concentrations.

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CONFLICT OF INTEREST STATEMENT

The study was partly funded by an unrestricted educational grant by Pfizer and an unrestricted educational grant by a non-profit foundation (de Stichting Vrienden van het JKZ). The sponsors had no role in the study design, data collection and analysis, nor the content of the manuscript. The corresponding author has full access to all data in the study. All authors declare no conflict of interest. This research was carried out at the Department of Pediatrics, Juliana Children's Hospital, The Hague, the Netherlands.

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Chapter 5

The effect of family-based multidisciplinary cognitive behavioral treatment on Health Related Quality of Life in Childhood obesity

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5 The effect of family-based multidisciplinary cognitive behavioral treatment on Health Related Quality of Life in Childhood obesity

ABSTRACT

Purpose
Childhood obesity can have a huge impact on both somatic as well as on psychosocial functioning. The aim of this study was to evaluate the effect of multidisciplinary treatment on obesity and Health Related Quality of Life (HRQOL).

Methods
Obese children were randomized to a multidisciplinary treatment (n=40, body mass index (BMI)-SDS; 4.2±0.7, age;13.3±2.0) or standard care (n=39, BMI-SDS 4.3±0.7, age;13.1±1.9). At baseline (T0), after 3 months (T1) of treatment and after 1-year follow-up (T2), data were collected for BMI-SDS and 2 European based validated questionnaires for assessing HRQOL (KIDSCREEN, DISABKIDS). Data of normal weight control group was collected once for comparison of HRQOL.

Results
At T0 obese children showed significantly lower HRQOL compared to their normal weight peers (p=0.02). A significantly reduced BMI-SDS was found for the intervention vs. obese control group at T1 (4.0±0.9 vs. 4.2±0.7, p=0.02) and T2 (3.8±1.1 vs. 4.2±0.7, p=0.03). HRQOL in the intervention group was improved at T2 compared to T0 (mean [95%CI]; 86.8[83.3-90.3] vs. 80.2[76.5-83.8], p<0.05), and unchanged in the obese control group. Parents reported a lower HRQOL for their obese children than the children themselves, with inter-class correlation coefficients for agreement varying between 0.669-0.847 for total HRQOL.

Conclusion
HRQOL is more impaired in obese children compared to their normal weight counterparts and parents reported a lower HRQOL than their children. Multidisciplinary treatment is effective in reducing BMI-SDS and improving HRQOL after 1-year follow-up.

Trial Registration
http://www.controlled-trials.com/ISRCTN36146436.

Key words: Health related quality of life; obesity; weight loss; children; adolescents; treatment; parents

INTRODUCTION

During the last three decades the prevalence of childhood obesity has increased dramatically in Western countries, with the Netherlands not making an exception. Consequence of the rising prevalence of childhood obesity is an earlier appearance of co-morbidities such as type 2 diabetes mellitus and cardiovascular diseases [1,2]. Besides these physiological consequences, obesity can also have adverse consequences for psychosocial well-being [3,4]. Research has revealed that children with obesity show impaired self-esteem and lower scores for Health Related Quality of Life (HRQOL) with regard to physical functioning [3], indicating that obese children experience a burden of their overweight status both in their physical performance as well as in their self-esteem. Furthermore, peer victimization of obese adolescents has been associated with low self-esteem, body dissatisfaction and social isolation [4]. Some authors even suggested that the HRQOL of severely obese children is comparable to that of children with cancer [5].

It appears that the HRQOL of obese children is particularly impaired concerning social and physical functioning in relation to the degree of overweight [3,6-11]. Children with obesity experience less social support from either their family or peers, and perceive more discomfort from their body weight on mobility in everyday life. Conflicting results have been reported concerning the effect of obesity on the psychological domain of HRQOL. While some investigators have found a weak [9] to moderate [8] association between obesity and the psychological domain of HRQOL, others reported no relationship at all [11,12]. The studies in which associations were observed were carried out in treatment seeking obese samples [8,9]. In obese children in community settings no adverse effect of their obesity on the psychological well-being was observed [11,12].

With respect to the parents' perspective on psychological QOL, parents view their children as having greater impairments in emotional functioning than children report themselves [9,12]. Indeed, studies examining the agreement between a child self-report and a parent proxy report showed consistently lower HRQOL scores for all domains from parent proxy assessment than from child self-report [7,12]. The reason for this difference is not yet clear [13].

The observations that childhood obesity has multifaceted consequences in both the physical and psychological area [1-4] has led to an increased inclusion of psychological aspects in the treatment of childhood obesity, apart from existing physical activity and nutritional advices. Reducing body weight for height (expressed as body mass index, kg/m^2 (BMI)) as well as improving HRQOL is the aim of most of these multidisciplinary treatments of children with obesity. The effects of such lifestyle interventions on maintenance of weight loss, however, are only small to moderate [14,15].
Furthermore, conflicting results have been reported on the effects of multidisciplinary treatment on HRQOL in obese children, probably due to the use of different outcomes for HRQOL. Some studies have reported increased HRQOL in all QOL variables after short-term multidisciplinary treatment, assessed by both a QOL questionnaire and a Pictorial Representation of Illness and Self Measure (PRISM) [16] or by means of a disease-specific quality of life measure [17]. Others, using the more general Pediatric Quality of Life Inventory (PedsQOL) [18] or the KINDL (German questionnaire for measuring quality of life in children and adolescents) [19], reported improvement in some of the QOL domains, but not in the psychological domain.

There is a need for further documenting the short- and long-term HRQOL of children receiving multidisciplinary treatment for obesity. Therefore, the primary goal of the current study was to assess the effect of a multidisciplinary cognitive behavioral treatment, focused on reducing BMI and improving HRQOL in obese children, assessed by both self-report and parent proxy report.

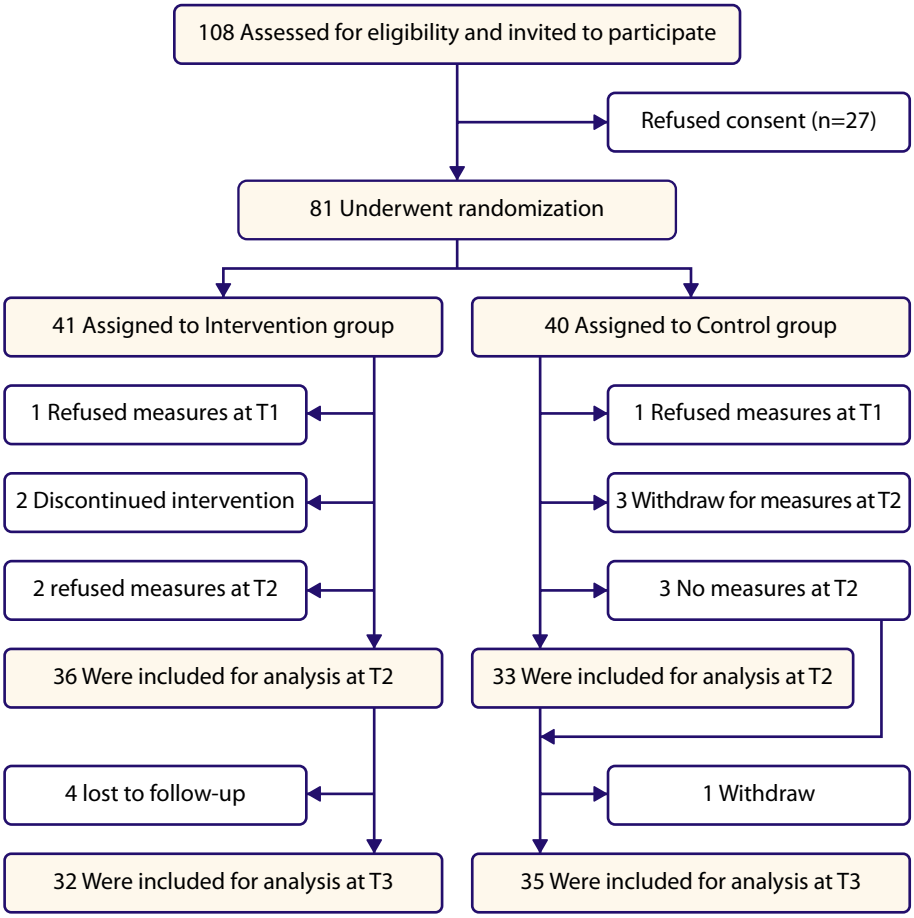
METHODS:

Study Design and Setting

This study is part of a randomized clinical trial on the effect of a multidisciplinary cognitive behavioral treatment on childhood obesity. For full details of the protocol the reader is referred to our previous report [20]. Here the effects of the treatment on HRQOL immediately after 3 months treatment and after 1 year are presented. Newly presented children with obesity according to Cole's reference values [21] aged 8-17 years, living in or close to the Hague and referred to a pediatrician for their obesity, were invited to participate.

Obese children who met inclusion criteria were stratified by gender and ethnicity ('North European' and 'Other') and randomized to the intervention (n=41) or control group (n=40) according to coin-tossing (figure 1). In order to obtain a similar size of the intervention and control groups, blocked randomization was applied with an allocation ratio of 1:1. Randomization was carried out by a member of the team who did not take part in the treatment. The children in the intervention group were divided into smaller groups of 10, depending on the child's age. Potential participants were excluded if their knowledge of the Dutch language was insufficient. Other exclusion criteria were use of medication that might have an effect on weight loss, medical co-morbidities that could affect participation (e.g. hypothyroidism, high dose of glucocorticoids, diabetes mellitus) or previous enrollment in another cognitive behavioral treatment program with the focus on reducing obesity. To enable comparison of the HRQOL data of the obese children with normal weight peers, 34 healthy age, gender and ethnicity matched children with normal weight, recruited by the youth health services (Jeugd GGD Haaglanden), were examined once. This study was conducted in agreement with the 'Declaration of Helsinki'. Approval was obtained from a regional medical ethical committee South West Holland. All parents and children gave their written informed consent.

Figure 1: *Flow diagram of participants through the study for the primary outcome measure (BMI-SDS)*



Multidisciplinary cognitive behavioral treatment

The multidisciplinary cognitive behavioral treatment of the intervention group consisted of a screening phase, followed by an intensive phase of three months and booster sessions thereafter for a total period of two years. In the screening phase the children with their parents were seen at two separate occasions individually by a dietitian (45 minutes/occasion), a child-physiotherapist (45 minutes/occasion), a child-psychologist (90 minutes/occasion) and once by a social worker (90 minutes).

During the screening phase a dietician provided nutritional advice on reducing caloric intake and, more importantly, on learning healthy eating behavior. A 3-day dietary recall (1 weekend day included) was used to get more insight in dietary habits of the children. Information was provided about nutrition and healthy eating behavior according to the traffic light nutritional list [22]. The traffic light nutritional list identifies several main food groups (fruits, vegetables, grains, milk and other dairy products, meat, fish, and others).

Foods within each group are color-coded reflecting the caloric density per average serving and Dutch standards for healthy nutrition. The colors are green for "go", orange for "approach with caution", and red for "stop". A child-physiotherapist evaluated the physical activity level of the children in the intervention group, based on a physical activity 3-days recall (1 weekend day included). The information from this recall was used for advice on how to increase and optimize physical activity during everyday life and to reduce sedentary activities. The role of the child psychologist was to help the children not only to reduce weight by learning cognitive behavioral techniques, but also to deal with and accept their own body.

The intensive phase of the treatment consisted of 7 group meetings for the children, 5 separate parent meetings and 1 meeting for parents together with their children. Meetings of 2½ hours per meeting were given biweekly. The main focus of the first two meetings with the children was on nutritional information of energy balance and healthy eating. During the remaining meetings with the children, several cognitive behavioral techniques were taught on self-control, coping and self-image, in order to maintain long-term lifestyle change and body weight reduction. The parent meetings addressed the topics of motivation for treatment of their children, including information on healthy nutrition, setting boundaries and how to help their children by giving positive feedback.

The control group was given an initial advice on physical activity and nutrition. After 1 year the children in the control group were offered to participate in the multidisciplinary cognitive behavioral treatment. The normal weight control group was measured only once at the beginning of the study.

Primary outcome

Data from the obese subjects were collected at baseline (T0), after the three months treatment (T1) and 1 year after baseline (T2). Weight to the nearest of 0.1 kg was measured using an electronic scale (SECA 911, Vogel & Halke, Hamburg, Germany) and height to the nearest of 0.1 cm with a stadiometer (Holtain, limited, Crymych, Dyfed, Britain) in underwear and barefoot. BMI was calculated as weight / height squared (kg/m^2). Subjects were classified as obese using BMI gender- and age specific international cut-off levels [21]. BMI was expressed as a standard deviation score (SDS) for Dutch references[23]. The 1980 reference data for weight and height were used to obtain a realistic view on the degree of obesity without data being biased by the increased prevalence rate of childhood obesity.

Secondary outcomes

The Health Related Quality of Life (HRQOL) of the children was determined by a generic questionnaire (KIDSCREEN) and a questionnaire for chronic conditions (DISABKIDS). The KIDSCREEN questionnaire was used to assess differences in HRQOL between obese and normal weight peers. The DISABKIDS questionnaire was used to evaluate the effect of the treatment on HRQOL in the obese children and their parents.

The KIDSCREEN questionnaire is suitable for children aged between 8-18 years and both a child as well as a parent proxy version are available. In this study only the child version was used to compare obese children with the children in the normal weight control group. The KIDSCREEN contains 52 questions addressing 10 domains of quality of life.

These domains are: QOL-physical, QOL-psychological, QOL-mood, QOL-self-perception, QOL-autonomy, QOL-parents, QOL-peers, QOL-school, QOL-bullying, QOL-financial. Each domain contains 3-7 items. Questions can be answered by choosing from a 5-point scale: options: never (1), almost never/ seldom, average/ sometimes, quite often, always (5). After adjusting the negative items, the total and domains scores of the questionnaire are expressed as a percentage between 0-100, with a higher percentage reflecting a better HRQOL. The KIDSCREEN questionnaire has demonstrated a Cronbach α reliability coefficient ranging between .77 and .89 for all ten domains [24], which is considered as a good reliability.

The DISABKIDS questionnaire is suitable for children aged between 4-18 years. In this study the DISABKIDS was used to compare the HRQOL of the obese children in the intervention group with the HRQOL of the children in the obese control group. Because the children's scores on HRQOL questionnaires are often higher than parental scores, we also used the parent version of the DISABKIDS questionnaire. The DISABKIDS questionnaire contains 37 questions divided over 6 subscales of 6-7 items each. In this study only the first five subscales (31 items) were used to calculate the HRQOL, because the last subscale focuses on medication use related to a disease. The five subscales that were included in this study are: QOL-life, QOL-day, QOL-feeling, QOL-other and QOL-friends. The questions could be answered by choosing from a 5-point scale: never (1), almost never/ seldom, average/ sometimes, quite often, always (5). After adjusting the negative items, the total and domains scores of the questionnaire were expressed as a percentage between 0-100, with a higher percentage reflecting a better HRQOL. The Cronbach α reliability coefficient of the child version of the DISABKIDS ranges between .70 to.87 for children aged 8-12 years and between .77 to.90 for children aged 13-16 years [24]. To our knowledge no results have been published of reliability coefficients concerning the parent proxy version of the DISABKIDS questionnaire.

Statistical analysis

Intention-to-treat analyses were performed using the Statistical Package for Social Science SPSS, version 17.0 for Windows (SPSS Inc., Chicago, IL, USA). An independent t-test was used to compare the obese children vs. the normal weight children at baseline. For comparison of the HRQOL domains at baseline between obese and normal weight children ANOVA analysis was used with Bonferroni correction for multiple testing and group as fixed variable. The total HRQOL score was analyzed separately. To determine the effect of time on the outcome variables within the groups ANOVA for repeated measures was performed for the domains with Bonferroni correction and for the total HRQOL and BMI-SDS separately with time as fixed variable. The effect of treatment on the total HRQOL scores and BMI-SDS were analyzed with ANOVAs for repeated measures with group and time as fixed variables. MANOVAs for repeated measures were used to determine the effect of treatment at T1 and T2 on HRQOL domains, both for the child and parent proxy report separately. In addition, an inter-class correlation coefficient (ICC) was used to describe the relationship between the child and parent proxy report for the total HRQOL scores and per domain. The level of significance for all analyses was set at $p<0.05$.

RESULTS

Treatment effect on BMI-SDS

The ANCOVA for the effect of the multidisciplinary treatment on BMI-SDS at T1 and T2, controlling for baseline measures, was statistically significant (p=0.02 and p=0.03, respectively), showing a reduction of BMI-SDS in the intervention group and no change in BMI-SDS in the obese control group.

HRQOL in obese vs. normal weight children

The results of HRQOL for the KIDSCREEN questionnaire for the intervention group, obese control group and normal weight control group at baseline are shown in table 1. No significant difference was found for age and gender between the obese and normal weight children. Total HRQOL was significantly lower in the obese group compared to the normal weight controls: (mean (SE) 83.0(0.9) vs. 86.7(1.1), p=0.02, respectively), as well as for the domains QOL-physical (mean (SE) 70.7(1.9) vs. 82.9(2.4), p<0.01, respectively) and QOL-self-perception (mean (SE) 69.0(1.9) vs. 85.891.9), p<0.01, respectively), indicating that obese children have impaired HRQOL, in particular for physical functioning and self-perception.

Table 1: *HRQOL of obese children vs. normal weight children at baseline*

Variable	Intervention group	Obese control group	Normal weight group
	M [95% CI]	M [95% CI]	M [95% CI]
Gender (M/F)	**18/22**	**19/20**	**14/20**
Age (years)	13.3 ± 2.0	13.1± 1.9	13.2 ± 2.4
BMI-SDS	4.2 ± 0.7‡	4.3 ± 0.6‡	0.5 ±1.4
QOL-Tot-Kid	81.4 [78.4;84.4]‡	84.7 [82.4;86.9]‡	86.7 [78.4;84.4]
QOL-physical	66.3 [61.5;71.0]‡	75.2 [69.5;80.9]‡	82.9 [78.0;87.8]
QOL-psychological	86.3 [82.9;89.8]	88.2 [84.1;92.3]	90.1 [87.3;92.9]
QOL-mood	83.9 [79.4;88.4]	84.7 [81.3;88.1]	87.1 [83.5;92.9]
QOL-self-perception	69.1 [63.7;82.9]‡	68.9 [63.4;74.3]‡	85.8 [819;90.8]
QOL-autonomy	83.1 [77.9;88.2]	87.3 [83.3;91.3]	87.3 [83.9;89.7]
QOL-parents	89.6 [85.6;93.5]	92.4 [90.0;94.9]	91.9 [89.0;90.7]
QOL-peers	79.6 [73.7;85.4]	85.0 [81.0;89.1]	85.0 [80.9;94.7]
QOL-school	87.0 [83.2;90.8]	92.2 [85.7;92.2]‡	82.4 [78.4;86.4]
QOL-bullying	86.3 [81.1;91.6]	88.7 [83.8;93.6]	90.9 [87.7;94.0]
QOL-financial	77.6 [69.9;85.3]	86.1 [80.2;92.0]	82.7 [76.3;89.2]

** The mean difference compared to obese control group is significant at the 0.05 level*

‡ The mean difference compared to normal weight control group at the 0.05 level

Treatment effect on HRQOL

The results of the DISABKIDS questionnaire in the intervention and obese control groups at T0, T1 and T2 are shown in table 2. At baseline no significant difference was found for total HRQOL nor for the domains between the intervention and obese control group. ANOVA of repeated measures for measuring differences in HRQOL over time within both groups, showed a significant increase of total HRQOL, QOL-life and QOL-feeling for the child report from T0 to T2 only for the intervention group. For the parent proxy a significant increase in total HRQOL as well as QOL-day was found for the intervention group at T2 vs. T0. The (M)ANOVAs for repeated measures for assessing differences in the effect of treatment over time on total HRQOL and the domains did not show a significant difference in mean change between the two groups, neither for the child report nor for the parent part of the questionnaire.

Table 2: *Short-term and Long-term results of DISABKIDS HRQOL*

Variable	Child Report		Parent Proxy	
	Intervention group	Obese control group	Intervention group	Obese control group
	M [95% CI]	M [95% CI]	M [95% CI]	M [95% CI]
T0 (baseline)				
Age (years)	13.3 ± 2.0	13.1 ± 1.9		
BMI-SDS	4.2 ± 0.7	4.3 ± 0.7		
QOL-Tot-Dis	80.2 [76.5-83.8]	82.8 [78.4;87.2]	74.1 [70.2;78.0]	79.8 [74.6;85.0]
QOL-life	82.2 [77.7;86.8]	84.7 [80.7;88.8]	84.8 [80.9;88.8]	86.4 [82.9;89.8]
QOL-day	81.5 [77.0-86.0]‡	81.8 [76.3;87.2]‡	70.9 [67.4;86.0]	73.6 [68.6;78.7]
QOL-feeling	76.0 [70.6;74.3]‡	78.8 [73.7;84.0]‡	68.8 [63.2;74.5]	71.1 [65.2;76.9]
QOL-others	87.5 [83.6;91.3]	87.0 [82.4;91.7]	82.9 [78.1;87.7]	83.7 [78.9;88.6]
QOL-friends	74.9 [70.7;79.0]	77.7 [73.6;81.9]	72.1 [66.9;77.3]	76.6 [71.4;81.7]
T1 (3 months)				
Age (years)	13.8 ± 1.8	13.4 ± 1.9		
BMI-SDS	4.0 ± 0.9*	4.2 ± 0.7		
QOL-Tot-Dis	84.1 [80.8-87.5]	83.9 [79.3;88.6]	77.9 [73.5;82.3]	80.5 [75.8;85.2]
QOL-life	87.4 [82.9;91.8]	88.0 [84.2;91.9]	84.9 [79.4;90.5]	86.3 [82.5;90.2]
QOL-day	82.5 [78.1-86.9]‡	85.8 [80.7;90.8]‡	73.6 [69.3;86.9]	74.0 [67.4;80.7]
QOL-feeling	84.5 [79.5;77.9]‡	80.1 [73.9;86.5]	73.0 [66.3;79.7]	75.3 [69.0;81.6]
QOL-others	89.1 [84.8;93.3]	87.7 [83.0;92.5]	81.9 [76.2;87.5]	86.3 [81.1;91.5]
QOL-friends	76.7 [72.6;80.7]	79.9 [74.6;85.2]	72.4 [67.4;77.5]	79.8 [74.3;85.3]
T2 (1-year follow-up)				
Age (years)	14.4 ± 1.8	14.0 ± 2.0		
BMI-SDS	3.8 ± 1.1*	4.2 ± 0.7		
QOL-Tot-Dis	86.8 [83.3-90.3]*‡	85.6 [81.2;89.9]	82.9 [78.9;87.0]*	81.6 [75.9;87.4]
QOL-life	90.1 [87.1;93.1]*	87.3 [83.5;91.0]	88.9 [85.7;92.2]	88.3 [83.8;92.8]
QOL-day	83.7 [78.5-88.8]	85.4 [80.7;90.0]‡	78.4 [73.9;88.8]*	78.8 [72.1;85.6]
QOL-feeling	87.0 [81.2;82.9]*‡	83.3 [77.8;88.8]‡	77.8 [71.8;83.8]	78.8 [73.6;84.0]
QOL-others	92.4 [89.1;95.7]‡	91.3 [87.8;94.7]‡	86.7 [82.7;90.7]	84.8 [78.9;90.7]
QOL-friends	78.9 [73.7;84.1]	80.4 [75.7;85.2]	78.9 [73.7;84.1]	77.8 [71.2;84.5]

** The mean difference compared to baseline is significant at the 0.05 level*

‡ The mean difference compared to parent proxy perspective at the 0.05 level

Child self report vs. parent proxy report

The inter-class correlation coefficient for the total HRQOL of the DISABKIDS questionnaire between child and parent report was 0.669 at baseline, 0.705 at T1 and 0.847 at T2. Those ICCs indicate that conformity in the scores of HRQOL between children and parents increased over time from 66.9% to 84.7% agreement. For the separate domains of the DISABKIDS questionnaire a poor to moderate ICC was found varying between 0.484 (QOL-day) – 0.640 (QOL-others) at baseline, between 0.492 (QOL-feeling) – 0.756 (QOL-friends) at T1 and between 0.553 (QOL-others) – 0.773 (QOL-friends) at T2, with lower scores found in the parent compared to child report.

DISCUSSION

This study aimed at evaluating the effect of a multidisciplinary cognitive behavioral treatment on BMI-SDS and HRQOL in obese children compared to standard care. Improvements in BMI-SDS were found after 3 months of multidisciplinary treatment and 12 months follow-up, with no changes in obese children receiving standard care. Concerning the short-term treatment effect on adiposity, similar conclusions were made in numerous previous reports on multidisciplinary lifestyle interventions [25-28]. Contrasting findings by others were however reported with regard to the long-term treatment effects on adiposity [25]. In contrast to our findings, in the latter study the reduced body weight after treatment was not further reduced in half of the subjects and even significantly increased in remaining half during the follow-up period [25].

Effect of Obesity on HRQOL

With respect to the impact of obesity on HRQOL, we found significantly lower total HRQOL scores in the obese vs. the normal weight children as well as lower domain scores of physical activity and self-perception. These findings confirm the results of others, also reporting lower total HRQOL in obese compared to normal weight children [6,9,29]. The lower QOL-physical activity score found in the obese vs. normal weight children in the current study was in agreement with other studies as well [6,9,10,30]. However, observations on differences between obese and normal weight peers for the psychological and the social domain of HRQOL are more diverse. While impaired social functioning was found in obese children by most other investigators [6,9,11], we observed significantly lower scores for the psychological domain in obese children. These contradictory findings might be attributed to differences in the definition of the HRQOL domains in the questionnaires used. So far many studies [6,7,9-11] have used the Pediatric Quality of Life Inventory (PedsQL 4.0) questionnaire for comparing HRQOL between obese and normal weight children, which is only partly comparable to the KIDSCREEN questionnaire.

Short-term treatment effect on HRQOL

Immediately after treatment HRQOL scores had already improved, though not significantly. In contrast, in previous studies a significant short-term effect on HRQOL scores was observed after multidisciplinary treatment [16,17,19]. This difference might be explained by the different methods used to determine HRQOL, or by the different treatment mode. While we used a validated generic questionnaire, in these prior studies also a (non-validated) obesity specific QOL questionnaire was used, and findings were reported after in-patient instead of out-patient treatment [16,17,19]. It is conceivable that a disease specific instrument is more sensitive to short-term change in HRQOL since it targets the areas critical for obesity. This difference in short-term sensitivity for treatment effect

between questionnaires, emphasizes the need for a obesity-specific module of DISABKIDS, as is available for several other diseases. In addition, the amount of weight-loss after the in-patient interventions was larger than observed in our patients. We speculate that that the short-term weight loss in our study was not pronounced enough to cause a statistically significant change in HRQOL.

Long-term treatment effect on HRQOL

Exploring the long-term effect of multidisciplinary treatment on HRQOL, we found a significant improvement after 12 months follow-up in the intervention group. At this time a better total HRQOL was found, as well as improved QOL for the specific domains of QOL-life and QOL-feeling.
Improved HRQOL after follow-up and not yet immediately after treatment have been reported in a previous study [17]. In this study two multidisciplinary treatment regimens for obese children were compared, one with and the other without the inclusion of psychological counseling. The improved HRQOL was only observed in the treatment group with psychological counseling. Taken together, these findings indicate that inclusion of psychological interventions and face-to-face contact with health professionals continued during follow-up seems to be important for the long-term improvement of HRQOL of obese children.

Child self report vs. parent proxy report

Comparing the children's self-reports with the parent proxy reports, we found significantly lower HRQOL scores reported by the parents. In addition, a poor to moderate inter-class correlation coefficient was found between the child and parent reports. This finding is in conformity with previous studies [7,9,12] that also reported lower parent proxy scores compared to child self-reports with poor parent-child agreement in a treatment seeking obese sample [12]. It is important to emphasize that previous studies found a similar ICC between normal weight children and their parents [9]. So parents of treatment seeking obese children are possibly more worried about their child than the children themselves or they may have a limited understanding of their child's experienced HRQOL. It is also possible that parents view HRQOL from a broader perspective than children do and are therefore better able to compare the HRQOL of their obese child with that of normal weight children. Either way, by using both children's self-reports and parent proxy reports a more complete impression of HRQOL is gained.

Limitations of the study

One of the limitations of this study is that our study population consisted of treatment seeking obese children, who may experience more impairment on their HRQOL than their obese peers in the community. Previous studies have shown varying results, some showing no significant differences between treatment seeking and community-derived obese children [9]. Other studies have reported lower scores of HRQOL in a treatment seeking sample [8,11]. A second limitation of the current study is that we did not use the PedQL 4.0 or an obesity-specific HRQOL questionnaire, used by most previous studies. Using the DISABKIDS and KIDSCREEN questionnaires, however, could also be regarded a strength, since this questionnaire is a European based and well validated questionnaire.

Strengths of the study

One important strength of the study is the randomized controlled design, studying the longitudinal effect of a multidisciplinary cognitive behavioral treatment on HRQOL in obese children compared to standard care. Whereas most other studies only report cross-sectional data or short-term treatment effect after non-randomized interventions, we randomly assigned our patients to an intervention and control group. By including a randomly allocated control group it was possible to detect if HRQOL further declined or remained stable when children were not treated. Additionally, the use of both self-reports as well as parent proxy reports in this study gives more information on the HRQOL of children and can help to determine at which level treatment can be improved. Furthermore, by assessing both self-report and parent proxy report it is possible to compare our results with previous studies using either one or both forms of report.

CONCLUSION

In conclusion, the obese children in our study showed significantly lower HRQOL compared to their normal weight peers. In particularly for physical functioning, lower HRQOL scores were found in obese children and agreement between child and parent report was moderate, with lower scores found by parent proxy report. In addition, obese children receiving multidisciplinary treatment showed a significant reduction of their BMI-SDS as well as significantly improved HRQOL after 1 year follow-up. However, although a significant weight reduction was found in the intervention group, the majority of the children were still obese after the multidisciplinary treatment. HRQOL assessment in children with obesity can help understanding the impact of obesity on everyday life and how it affects the child's well-being. Results of these HRQOL measurements can be used to improve treatment of obese children; for example the most impaired domains of HRQOL can be considered in greatest need of extra attention in the multidisciplinary treatment. In addition, more longitudinal studies on the effect of multidisciplinary treatment on HRQOL in obese children are needed to explore how treatment programs for obesity can be improved.

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CONFLICT OF INTEREST STATEMENT

All authors declare no conflict of interest. This research was carried out at the Department of Pediatrics, Juliana Children's Hospital, The Hague, the Netherlands.

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Chapter 6

The Predictive Value of the Individual Components of the Metabolic Syndrome for Insulin Resistance in Obese Children

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6 The Predictive Value of the Individual Components of the Metabolic Syndrome for Insulin Resistance in Obese Children

ABSTRACT:

Background/Aims

The usefulness of the concept of the Metabolic Syndrome (MS) in its current form was recently questioned and its association with insulin resistance is unknown. We assessed whether a multivariate model based on all components of MS expressed on a continuous scale would be a better predictor of a common marker of insulin resistance than the current dichotomous MS definitions (Cook, de Ferranti, IDF).

Methods

Data from 78 obese Dutch teenagers (13.0±2.1yr) were used for model development and the model was validated in 40 obese Hindustani children (12.6±2.0yr). The MS components and HOMA-IR were expressed as standard deviation scores (SDS), based on gender- and age-specific reference values.

Results

The prevalence of MS was 36% (Cook), 65% (De Ferranti) and 18% (IDF), with low mutual agreement. None of these dichotomous models were significant predictors for increased HOMA-IR SDS. The multivariate model incorporating the MS components expressed as SDS explained 58% of the variance of increased HOMA-IR SDS. In the validation group the predicted and observed HOMA-IR SDS (2.4±1.2 vs. 2.6±2.2) did not differ significantly.

Conclusion

A multivariate prediction model based on the MS components expressed as SDS has a good predictive value for increased HOMA-IR SDS.

Keywords: metabolic syndrome; children; prediction model; obesity; HOMA.

INTRODUCTION

Since the 1980s the prevalence of childhood obesity has increased dramatically worldwide (1-3). For example, in the Netherlands the prevalence of overweight and obesity in children (4-16 years) has more than tripled (from 3.9 to 14.5%) in boys in the period 1980-2003 and more than doubled (from 6.9 to 17.5%) in girls, and is still increasing (4). Several studies have demonstrated that 50% of children and 80% of adolescents with obesity become obese adults (5;6). In adults, obesity is associated with a higher risk for developing type 2 diabetes mellitus and cardiovascular disease (7-10), and in children and in adolescents obesity is associated with increased prevalence of hypertension, dyslipidemia and impaired glucose metabolism (11-14). The clustering of these risk factors was first reported in 1988 by Reaven as Syndrome X. Originally, the syndrome focused on the association with hyperinsulinemia and insulin resistance (15) , also in obese children (16). Furthermore, longitudinal studies have suggested that the Syndrome X in children and adolescents predicts the developing cardiovascular disease and type 2 diabetes mellitus in adulthood life (13;17-19). Therefore the syndrome was renamed as Metabolic Syndrome (MS).

For the pediatric age group several definitions have been proposed, with modifications of adult definitions most commonly used (16;20-24). Hyperinsulinenia is not included in most definitions. Consensus on the cut-off levels of the separate components of the MS for pediatric patients has still been difficult to obtain. One of the reasons is that in children and adolescents these cut-off levels are not only influenced by gender, but also by age and pubertal stage (20;22;25). Previous studies have shown that even in the same study group the prevalence of the MS varies considerably depending on the definition chosen (25-27). Furthermore, the dichotomous concept of the MS was recently questioned (28;29), and a recent WHO report has expressed doubt on the usefulness of the concept of MS in its current form (29). There is no accepted central underlying mechanism of the MS, although insulin resistance (10) and central obesity (30) have both been proposed to play this role.

In view of this current opinion on the limited usefulness of the MS, new strategies to overcome at least part of its limitations are needed. Insulin resistance is an independent predictor of cardiovascular disease and type 2 diabetes (31-34). In addition is was recently shown to be the best predictor of MS in first-degree relatives with type 2 diabetes (35). This study aimed to: 1) investigating the predictive value of the traditional parameters of MS as assessed by current dichotomous definitions of MS (Cook et al. (20), de Ferranti et al (22) and IDF (36;37)) for insulin resistance; and 2) develop a multivariate model incorporating all components of the MS expressed as standard deviation scores (SDS) to predict insulin resistance in obese Dutch children, and validate this in an independent group of obese Hindustani children.

METHODS

Subjects

Clinical data were collected of children with obesity (based on the cut-off level described by Cole et al. (1)) who were referred to two pediatric clinics (Juliana Children's Hospital/ HagaHospital (JKZ), the Hague, and Leiden University Medical Center (LUMC), Leiden. The age range was limited to 10.0-18.0 years, since MS is difficult to determine in children younger than 10 years (36;37). Children were excluded when their obesity was caused by an underlying medical condition or medication use. For developing the prediction model for insulin resistance, patients were divided into two groups: the first group included children of Dutch ancestry (n=78) and the other group children of Hindustani origin (n=40). The prediction model was based on the Dutch children and validated in the Hindustani children. Ethnicity was determined according to self-reports by the parents.

Definitions of the Metabolic Syndrome

The MS was defined according to the three most often used definitions for the pediatric age group by other research groups (Cook et al.(20), De Ferranti et al.(22), IDF(36;37) (Table 1)). The MS was considered present when three or more components were abnormal in the definitions of Cook and de Ferranti. According to the definition of the IDF, subjects were classified as MS when their waist circumference (WC) was increased and two or more of the other parameters were abnormal. In all definitions the Dutch gender- and age-specific WC diagrams were used for classification of central obesity (38). In the definitions of both De Ferranti and Cook the age-, height- and gender-specific percentiles of the National High Blood Pressure Education Program (NHBPEP)(39) were used for blood pressure. In the definition of the IDF the adult criteria for hypertension were used. The three definitions used different cut-off levels for impaired fasting HDL and fasting triglycerides (TG). Cut-off levels for impaired fasting glucose (FG) are the same in the definitions of De Ferranti and Cook. The IDF definition uses a different cut-off level for impaired FG (Table 1).

Table 1: *Definitions of the Metabolic Syndrome according to Cook, de Ferranti and IDF*

CRITERION	DEFINITIONS		
	Cook et al.[20]	**De Ferranti et al.[22]**	**IDF[37]**
	≥3 of the 5 criteria below:	≥3 of the 5 criteria below:	WC ≥ 90th percentile, age ≥10 yr and ≥2 of the other 4 criteria:
Waist Circumference (cm)	≥ 90th percentile (age-, sex specific)	≥ 75th percentile (age-, sex specific)	≥ 90th percentile (age-, sex specific)
Blood Pressure (mmHg)	≥ 90th percentile (age-, sex-, height specific)	≥ 90th percentile (age-, sex-, height specific)	SBP ≥ 130 and/or DBP ≥ 85
HDL (mmol/L)	HDL ≤ 1.04	HDL < 1.30	HDL < 1.03
Triglycerides (mmol/L)	TG ≥ 1.24	TG ≥ 1.1	TG ≥ 1.7
Glucose Intolerance (mmol/L)	FG ≥ 6.1	FG ≥ 6.1	FG ≥ 5.6

Measurements

Weight was measured to the nearest of 0.1 kg using an electronic scale (SECA 911, Vogel & Halke, Hamburg, Germany) and height to the nearest 0.1 cm with a stadiometer (Holtain, limited, Crymych, Dyfed, Britain) in underwear and barefoot. The Body Mass Index (BMI) was calculated as weight/height squared (kg/m^2). Subjects were classified as obese using BMI international gender- and age-specific cut-off levels developed by Cole et al. (1). The WC (in cm) was measured with an anthropometric tape midway between the lower rib margin and the iliac crest at the end of gentle expiration. Blood pressure was determined in a relaxed sitting position measurement with an electronic device (Criton Dinamap, No. 8100), in duplicate; the last measurement was used for further analysis.

Laboratory analysis

With the subject in the supine position, blood samples were taken by venipuncture after an overnight fast. Before blood sampling, the study participants and their parents were asked to confirm the fasting state. Fasting plasma HDL, TG and FG were collected with BD vacutainers (LH PST II Plus Blood Collection Tubes, BD Belliver Industrial Estate, Plymouth, UK). Plasma fasting insulin (FI) was sampled with Vacuette 2.5 mL Z Serum Sep Clot Activator (Greiner Bio-One GmbH, Kremsmüsterm Austria). Analysis for fasting plasma HDL, TG and FG was conducted by the hospital laboratory of the HagaHospital (The Hague, the Netherlands) and FI by the laboratory of the Leiden University Medical Center (Leiden, the Netherlands). HDL was analyzed by homogenic enzymatic colorimetry, TG by automatized colorimetry, all determined by bynchon Lx20 Pro/ unicel DXC 800 (Beckman Couter, Brea, US) and FG was analyzed by the glucose-oxidase method.
FI was analyzed by the Immulite 2500 immunoanalyser (Siemens healthcare Diagnostics, Deerfield, IL, US).
An index for insulin resistance was calculated according to the HOMA-IR formula: fasting insulin (μU/mL) x fasting glucose (mmol/L)) / 22.5 (40). Although a hyperinsulinemic-euglycemic clamp is considered to be the golden standard for determining insulin resistance, the non-invasive HOMA-IR model is considered a useful tool to assess insulin resistance in epidemiologic studies (40).

Statistical analyses

The analysis was performed using the Statistical Package for Social Science (SPSS), version 17.0 for Windows (SPSS Inc., Chicago, IL, USA) and the level of significance was set at $p<0.05$. Data were checked for normality before analysis using descriptive statistics and histograms. Data are expressed mean ± standard deviation (continuous variables) and as count and percentage (categorical variables). Independent t-tests were used for comparison of the 'Dutch' and 'Hindu' subgroups with continuous data and the Chi-square test for comparison with categorical data. Standard deviation scores (SDS) were calculated for the individual parameters of the MS, based on gender- and age-specific reference values, for WC (38), HDL (41), TG (41), FG (42), systolic blood pressure (SBP) and diastolic blood pressure (DBP) (43;44). Standard deviation scores for HOMA-IR (HOMA-IR SDS) were calculated, based on gender- and age-specific reference values (42). In order to test the agreement between the dichotomous definitions of MS the weighted kappa was used. The weighted kappa ranges between 1 (perfect agreement) and 0 (no agreement).
In general values less than 0.40 indicate poor, between 0.41-0.60 indicate moderate, between 0.61-0.80 indicate good and above 0.81 very good agreement.

To establish the predictive value of the three dichotomous definitions of the MS (Cook, de Ferranti, IDF) separate linear regression models were performed, with HOMA-IR SDS as dependent variable. The prediction model with the SDSs of the individual components of MS was developed by means of multiple linear regression in the group of Dutch children. Because fasting glucose is used to calculate the HOMA-IR, the model was also conducted without FG-SDS. The coefficients of the first model were used to calculate the predicted HOMA-IR SDS for all children. Differences between observed and predicted HOMA-IR SDS were expressed in terms of Studentized residuals. The residual is calculated as the observed HOMA-IR SDS minus the predicted HOMA-IR SDS for each observation, and the Studentized residual is the residual divided by its SE. For the validation of both models data was used from 40 Hindustani children, who fulfilled the inclusion criteria. Paired sample t-test was used to determine a significant difference between the observed and predicted HOMA-IR SDS in the Hindustani children. Pearson correlation was also used to assess the correlation between the observed and predicted HOMA-IR SDS in the model validation subgroup.

RESULTS

The characteristics of the 78 Dutch children (31 boys (40%)) studied and of the 40 Hindustani children (16 boys (40%)) are listed in Table 2. There is a trend towards a younger age in the group with Hindustani children. The FG-SDS is significantly higher and a trend towards a lower WC-SDS is found in the 'Hindu' compared to the 'Dutch' group.

Table 2: *Subject characteristics of the Dutch group of obese children group used for constructing the model and of the Hindustani validation group*

	DUTCH (N=78) Mean ± SD	HINDUSTANI (N=40) Mean ± SD	P-VALUE*
Age (years)	13.5 ± 2.1	12.6 ± 2.0	NS (0.06)
Weight (kg)	84.0 ± 17.5	80.8 ± 19.4	NS
Height (cm)	161.9 ± 9.8	157.7 ± 11.0	0.03
BMI (kg/m^2)	31.7 ± 3.9	32.0 ± 4.3 NS	NS
BMI-SDS	3.0 ± 0.7	3.1 ± 0.7	NS
WC (cm)	97.0 ± 10.6	91.6 ± 10.7	0.01
WC-SDS	4.4 ± 1.3	3.9 ± 1.2	NS (0.06)
SBP (mmHg)	125 ± 11	126 ± 12	NS
SBP-SDS	1.6 ± 1.0	1.8 ± 1.0	NS
DBP (mmHg)	66 ± 8.5	65 ± 9.6	NS
DBP-SDS	-0.0 ± 0.8	0.1 ± 0.9	NS
HDL (mmol/L)	1.2 ± 0.3	1.1 ± 0.2	NS
HDL-SDS	-0.8 ± 1.0	-0.9 ± 0.7	NS
TG (mmol/L)	1.2 ± 0.9	1.0 ± 0.4	NS
TG-SDS	0.3 ± 1.0	0.2 ± 0.5	NS
FG (mmol/L)	5.0 ± 0.4	5.2 ± 0.4	<0.01
FG-SDS	-0.2 ± 1.0	0.3 ± 1.0	0.02
FI (mU/L)	17.2 ± 11.2	20.7 ± 10.3	NS
HOMA-IR index	3.9 ± 2.7	4.8 ± 2.4	NS (0.06)
HOMA-IR SDS	1.9 ± 2.5	2.6 ± 2.2	NS

** p-value < 0.05 is considered statistically significant, NS= not significant.*

In the Dutch group the highest prevalence rate of the MS was found using the definition of De Ferranti (65%), followed by Cook (36%), and the lowest prevalence rate was found according to the IDF criteria (18%) (Table 3). The weighted Kappa, used to test the agreement between these definitions was 0.56 (Cook vs. IDF), 0.46 (De Ferranti vs. Cook) and 0.21 (De Ferranti vs. IDF), thus the agreement between these definitions was poor to moderate. Mean BMI-SDS in subjects with vs. without the MS according to the definition of De Ferranti was not significantly different (3.1 ± 0.8 SDS vs. 3.0 ± 0.7 SDS, respectively). A significantly higher BMI-SDS was found for children with vs. without the MS by Cook (3.3 ± 0.7 SDS vs. 2.8 ± 0.8 SDS, p=0.03) and by the IDF criteria (3.5 ± 0.8 SDS vs. 2.9 ± 0.6 SDS, p=0.01).

Table 3: *Prevalence of the metabolic syndrome and the frequencies of its criteria according to the three proposed definitions*

COOK ET AL.[20]	FREQUENCY N (%)	DE FERRANTI ET AL.[22]	FREQUENCY N (%)	IDF[37]	FREQUENCY N (%)
≥3 of the 5 criteria below:	28 (36)	≥3 of the 5 criteria below:	51 (65)	WC ≥ 90th percentile, age ≥10 yr and ≥2 of the other 4 criteria:	14 (18)
WC ≥ 90th percentile	78 (100)	WC ≥ 75th percentile	78 (100)	WC ≥ 90th percentile	78 (100)
BP ≥ 90th percentile	50(64)	BP ≥ 90th percentile	50 (64)	SBP ≥ 130 mmHg and/or DBP ≥ 85 mmHg	23 (30)
TG ≥ 1.24 mmol/L	23(30)	TG ≥ 1.1 mmol/L	31 (40)	TG ≥ 1.7 mmol/L	13 (17)
HDL ≤ 1.04 mmol/L	22(28)	HDL < 1.30 mmol/L	51 (65)	HDL < 1.03 mmol/L	21 (27)
FG ≥ 6.1 mmol/L	1(1)	FG ≥ 6.1 mmol/L	1 (1)	FG ≥ 5.6 mmol/L	4 (5)

Increased HOMA-IR SDS was not significantly predicted by the dichotomous definitions of MS. This is also reflected in the low explained variance in increased HOMA-IR SDS by the three definitions; 17.8% (2.3SE) according to De Ferranti, 16.3% (2.3SE) according to Cook and 16.1% (2.3SE) according to IDF. Because the risk is expressed as 'present' or 'not present', with no distinction in severity of increased metabolic risk, this finding indicates that by dichotomizing increased metabolic risk much predictive information is lost.

The multiple linear regression model incorporating the SDSs of the individual components of the MS as predictive variables and HOMA-IR SDS as outcome variable is shown in Table 4. The most important predictor of HOMA-IR SDS (apart from FG-SDS) is WC-SDS. The explained variance of the model with FG-SDS is 58%, with a standard error of 1.8 and is described by the following multiple linear regression equation: HOMA-IR SDS = 2.2 + 0.9 x Gender (male=0, female=1) –0.3 x Age (year) +1.0 x FG-SDS + 0.7 x WC-SDS - 0.8 x DBP-SDS + 0.6 x SBP-SDS + 0.7 x TG-SDS – 0.2 × HDL-SDS.

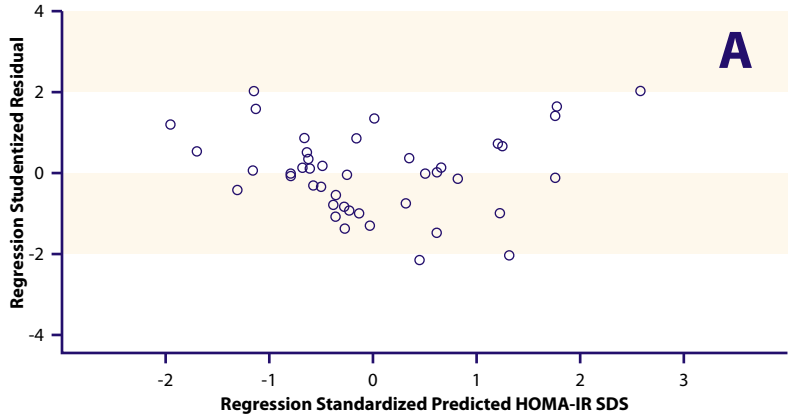
Table 4: *Prediction model for increased HOMA-IR SDS according to the enter procedure. Rank order is based on a backward procedure*

MODEL	PREDICTOR	COEFFICIENT [95%CI]	RANK
Linear Regression with all SDSs in the model	(constant)	2.2 [-4.2;8.6]	
	Gender	0.9 [-0.3;2.1]	
	Age	-0.3 [-0.6;0.0]	
	FG-SDS	1.0 [0.3;1.6]	1
	WC-SDS	0.7 [0.2;1.2]	2
	DBP-SDS	-0.8 [-1.7;0.1]	3
	SBP-SDS	0.6 [-0.2;1.4]	4
	TG-SDS	0.7 [-1.1;2.6]	5
	HDL-SDS	-0.2 [-0.9;0.5]	6

The multiple linear regression equation for HOMA-IR SDS without FG-SDS in the model has an explained variance of 46%, with a standard error of 2.0 and can be described as follows: HOMA-IR SDS = - 0.8 + 0.8 x Gender (male=0, female=1) –0.2 x Age (year) +1.1 x WC-SDS - 0.8 x DBP-SDS + 0.7 x SBP-SDS + 0.8 x TG-SDS – 0.3 × HDL-SDS.

For the mathematical validation of both prediction models a Studentized residual plot is used to identify outliers, nonlinearity, and non-constant error variants in the prediction model. The observed randomly clustered observations imply that there is no heterogeneity in the Dutch group with respect to relevant importance of the different predictors (Figures 1A and 2A). The paired student t-test to determine the difference between observed HOMA-IR SDS (2.6 ± 2.2) and predicted HOMA-IR SDS (2.4 ± 1.2) in the Hindustani children was not statistically significant (p=0.550). This indicated that HOMA-IR SDS of these children can be predicted by the model for predicting HOMA-IR SDS, based on the data in the Dutch children. Also the correlation between the observed and the predicted HOMA-IR SDS in the Hindustani children is statistically significant ($r=0.540$, $p<0.01$). In addition, the plot of the Studentized residual vs. the predicted HOMA-IR SDS in the validation group (Figures 1B and 2B) showed a similar pattern of randomly clustered observations as in the plot of the Dutch group.

Figure 1: *Studentized rediduals vs. predicted HOMA-IR SDS in the Dutch children with obesity (A) and the validation group (B) according to the derived prediction model including all SDSs of the individual parameters of MS*



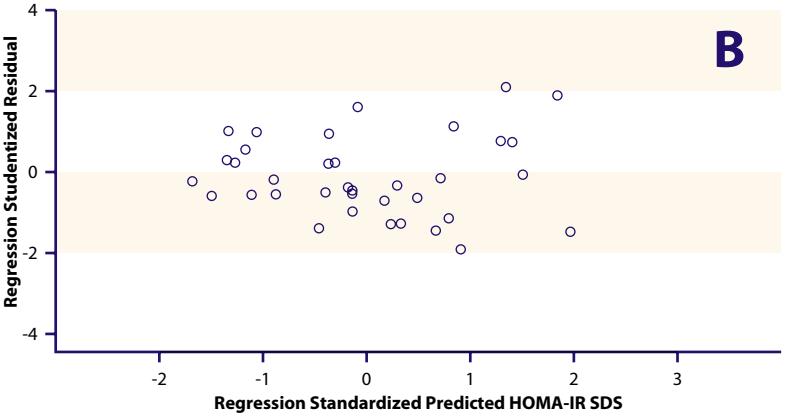
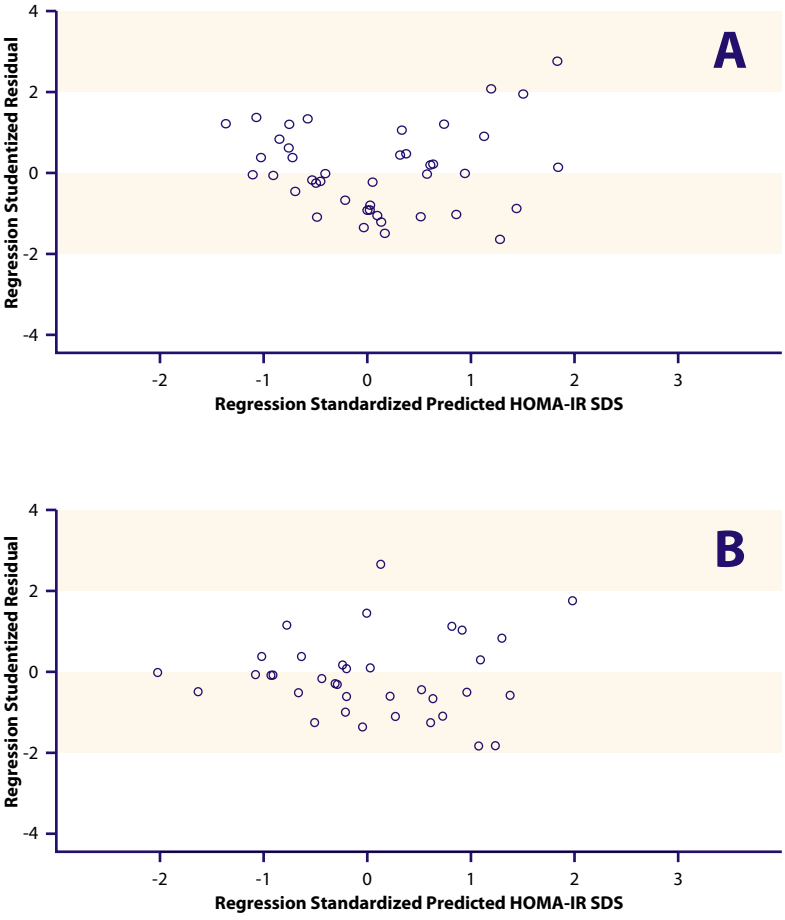


Figure 2: *Studentized rediduals vs predicted HOMA-IR SDS in the Dutch children with obesity (A) and the validation group (B) according to the derived prediction model including all SDSs of the individual parameters of MS except FG-SDS*



DISCUSSION

The results of our study demonstrate a different impact for the individual components of the metabolic syndrome (MS) on increased insulin resistance. The regression model with all the standard deviation scores of the individual components of MS in the model, showed an explained variance of 58%. From the individual variables of the MS, not included in the HOMA-IR index, the standard deviation score of WC provided to be the best predictor for increased insulin resistance, confirming the previously reported superior role of the WC in predicting health risk (45;46).

The predictive value of the dichotomous definition of the MS on increased HOMA-IR SDS was poor (16.1-17.8%) and not statistically significant. Furthermore, no significant difference was found for BMI-SDS between children with and without MS by the definition of De Ferranti, suggesting that this definition provides the least information on which child is most at risk.

It is now widely recognized that the definition of the MS in its current form has limitations. A major disadvantage of the MS definition is its dichotomous character. As pointed out by the WHO (29), dichotomization of a health risk makes it impossible to determine the absolute risk of a subject and to assess whether this health risk increases or decreases. In addition, in children the cut-off levels of the individual components of the proposed definitions of the MS are age-, and gender-dependent. Since no consensus exists on the optimal cut-off values for the parameters of the MS and reference values are often lacking for age and gender, prevalence rates are study design dependent. As a result, widely varying prevalence rates have been found, as shown by us (20-55%) and others (13-50%) (16;22;24-27;47;48) in the same study population, when different definitions are used. As a consequence it is difficult to compare the results of prevalence rates of the MS between different study populations.

A previously suggested alternative for the dichotomization of the metabolic risk is to calculate a continuous metabolic risk score, including fat mass (DXA), waist circumference, BMI, HOMA-IR and systolic blood pressure (28). However, the metabolic risk score in this study was calculated by subtracting the sample's mean from the individual mean, which was then divided by the standard deviation of the sample mean. By definition the mean score for metabolic risk of the study sample was zero. The sum of the sample-based Z-scores was divided by the number of variables, included in the risk score. So again a relative risk is obtained which is only applicable for the studied sample at the time of data collection. Another problem not solved by this alternative approach, is that by using the average of the Z-scores a similar weight is given to the Z-scores of the individual components. In contrast, the frequency and impact of the specific components are probable not equivalent.

To overcome these obstacles we propose to express the individual metabolic risk variables as standard deviation scores, based on gender- and age specific reference values. In this way changes can be detected easier, which provides the clinician with a long-term perspective on change in health risk. This will help the clinician in deciding about the frequency of consultations and the level of care to be provided to the child. Furthermore, by using a regression model to predict increased health risk, differences in the impact of the individual components of MS on health risk are taken into consideration. A similar approach was used by Ranke et al to predict growth velocity during growth hormone treatment based on a series of clinical parameters (49).

We determined the predictive value of the SDSs of the individual MS components on increased insulin resistance. As expected, we found a different impact for the individual MS parameters on increased HOMA-IR SDS. However, although this model showed a quite reasonable predictive value (58% with and 46% without FG-SDS), the predictive power of the presence and severity of the MS for type 2 diabetes mellitus in later years is unknown. Moreover, during childhood, it is known that the degree of insulin resistance varies, with many unknown influencing factors. For that reason, it is not unexpected that a substantial part of the variance in the prediction model remains unexplained.

To validate our prediction model for increased HOMA-IR SDS, we used the data of a separate group of children meeting the same inclusion criteria, but of different ethnic origin. In this group the predicted and observed HOMA-IR SDSs were comparable and their correlation was statistically significant. Also the Studentized residual plot showed randomly clustered observations, implying no heterogeneity in the validation group with respect to relevant importance of the different predictors. These findings indicate that our prediction model may be useful for predicting increased HOMA-IR SDS in other groups of obese children.

We are aware that our study has some limitations. The sample sizes of both groups were relatively small for constructing and validating a prediction model. However we feel that despite this limitation our study can offer a valuable contribution to the discussion on ways to improve the concept of the MS for predicting which obese child is most at risk for developing morbidity. Furthermore, data from a clinical sample of obese subjects may be influenced by selection and referral bias and may therefore not be representative for all obese children in the general population. However, obese children, referred to a pediatrician, are probable most at risk for developing obesity related co-morbidity. Future research with a larger sample size is recommended to validate and refine our model.

In conclusion, the variation in prevalence rates for the MS between three dichotomous definitions in the same pediatric study population is high, and mutual agreement is poor. Since the individual parameters of the MS are age-dependent and gender-dependent they can better be expressed as SD scores than be compared with fixed cut-off levels. We developed a model for predicting increased insulin resistance, taken into considerations the different impact of the standardized components of the MS. We speculate that using such a model to predict obesity-related co-morbidities may prove superior to the current definitions, because it provides an indicator for the severity of MS and a tool for assessing amelioration or deterioration of metabolic risk factors in obese children and adolescents.

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CONFLICT OF INTEREST STATEMENT

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Chapter 7

General Discussion

7 General Discussion

The general aim of the studies described in this thesis was the effect evaluation of a family-based multidisciplinary cognitive behavioral treatment on several domains related to childhood obesity compared to standard care. The primary outcome parameters were the treatment effect on total obesity (BMI-SDS) and abdominal obesity (WC-SDS). Other domains of interest were the effect of the above-mentioned treatment on glucose homeostasis, inflammatory state, secretion of gastrointestinal hormones involved in food regulation, physical fitness and Health Related Quality of Life (HRQOL). Furthermore, we aimed to evaluate the effect of the metabolic consequences of childhood obesity on increased health risk in terms of insulin resistance. In this chapter the results of these studies will be considered in a broader perspective. First the main findings of these studies will be reviewed in relation to the literature. Next, possible causes for the modest weight reduction after lifestyle interventions in the obese children will be discussed. Subsequently, the predictive value of impaired anthropometric and metabolic variables on future health risk will be addressed. This chapter will conclude with a discussion on clinical relevance and future research perspectives.

RESULTS OF MULTIDISCIPLINARY COGNITIVE BEHAVIORAL TREATMENT OF OBESE CHILDREN

Childhood obesity is a worldwide expanding problem and now poses one of the greatest public health challenges for the next decades, along with its associated co-morbidities. In the battle against childhood obesity behavioral lifestyle interventions, combined with parental involvement, are preferred over standard care or self-help (1). The results of behavioral lifestyle interventions on obesity and associated co-morbidities are promising (2-7), however, the intermediate and long-term follow-up effects are uncertain (8;9).

The results discussed in chapter 3 show a positive short-term (3 months), intermediate (1 year follow-up) and long-term (2 years follow-up) treatment effect on total obesity (BMI-SDS) as well as abdominal obesity (WC-SDS). This latter finding is of special importance, since it has previously been reported that health risk is increased by the combination of increased BMI-SDS alone and a WC > 90th percentile for age and gender, rather than by an increased BMI-SDS *per se* (10). In the same chapter we also showed that weight reduction after lifestyle treatment improved physical fitness, while a constant degree of obesity, as found in our obese control group, was associated with a significantly decreased physical fitness. This finding of an improved physical fitness in our intervention group is not only important for their health status, but also for their psychological wellbeing.

In chapter 5 we showed that obese children experience a lower HRQOL especially for the domains related to physical fitness and self-perception, as was reported previously (11-14). It is important to mention that, although obese children significantly reduce their adiposity after lifestyle treatment, they remain on average still obese. In view of this, findings like a reduced WC-SDS, improved physical fitness and better HRQOL after modest weight loss are important. Measurement of waist circumference, a simple test for physical fitness and the completion of a short HRQOL questionnaire during follow-up visits of obese children and their family after treatment could be motivating and helpful tools, both for pediatricians and general practitioners.

In addition, although modest weight reduction by lifestyle intervention slightly elevates ghrelin levels, as shown in chapter 4, it did not affect PYY or GLP-1 concentrations. Also the increased inflammatory state in the obese children compared to normal peers was not significantly altered after lifestyle treatment in our study (chapter 3), while others did find a significant treatment effect (7;15). It is therefore conceivable that a more substantial average weight reduction of ≥ 0.5 BMI-SDS would have had a more pronounced effect on gut hormone concentrations and inflammatory state.

POSSIBLE CAUSES OF MODEST RESULTS OF LIFESTYLE INTERVENTIONS

It is known that numerous factors contribute to obesity, including genetic, environmental, biochemical, psychological and physiological factors. This complex multi-factorial causality underlying childhood adiposity, makes it unlikely that a single treatment will be successful for all children with obesity. Also, the socio-economic status and ethnic diversity should be taken into consideration in future attempts to improve the treatment of childhood obesity. To improve long-term follow-up results, it may be considered to offer treated pre-pubertal children a modified lifestyle intervention again, once they enter puberty.

Besides modest weight reduction as a result of multidisciplinary lifestyle interventions, another known problem in this kind of weight reduction treatment programs is the high dropout rate during treatment and follow-up (8). In our study repeated booster sessions were scheduled during the whole follow-up period of 2 years, but we also found decreasing adherence of the participants over time, with the highest dropout rate during the first 12 months (8 children). In the second year of the intervention only one additional child was lost to follow-up. To overcome this problem, an increased frequency of booster sessions, such as every other month during the first year and 3 additional ones during the second year of follow-up might be beneficial, partly because of the effect of social peer pressure in the treatment groups. Also frequent email communication and an attractive interactive website where children can ask questions answered by health professionals and chat with their obese peers might be helpful.

In spite of these additional strategies to improve treatment results by motivating obese children to change their lifestyle, the real problem lays in the difficulty to change the environment of these children. Historically, a fat child meant a healthy child, one who was likely to survive the rigors of undernourishment and infections (16). Moreover, people had to deal with fluctuating food availability during the year and from year to year. In this light it was beneficial to evolve a mechanism to protect man from extinction during long periods of hunger. In addition, human energy regulating systems are extraordinarily precise under normal conditions and a positive energy balance of only 120 kcal per day will produce a 50 kg increase in body weight over a period of 10 years (16). Thus, any factor that raises energy intake or decreases energy expenditure by even a small amount will cause obesity in the long-term (16). In today's society of industrialized countries, not only energy intake has increased, but also food is always available without periods of shortage. Furthermore, a sedentary lifestyle has become more common. In view of this, the rapidly increasing prevalence rates of childhood obesity in a genetically stable population during the last few decades, can be largely attributed to adverse environmental factors in combination with an evolutionary conserved tendency to favor obesity. It is, therefore, unrealistically optimistic to expect that the battle against childhood obesity can be won without fundamental changes in social environment.

EFFECT OF CHILDHOOD OBESITY ON ADULT HEALTH

Childhood obesity is of particular interest, because of possible long-term associations with adult overweight and subsequently associated morbidity. There is strong evidence that obesity during childhood increases the risk of obesity during adulthood considerably (17). In addition, a large population based cohort study found that higher childhood (7-13 years) BMI values elevated the risk of developing coronary heart disease (CHD) in adulthood (≥ 25 years) (18). Furthermore, in chapter 6 we showed that increased WC-SDS and FG-SDS were significant predictors for increased HOMA-IR SDS. So, unless aggressive new treatment modalities will be developed to change obesity trends, present-day childhood obesity will have a substantial effect on public health, reaching far into the future.

The CHD Policy Model, in which the prevalence of 35-year-old obese adults in 2020 is estimated, is used to predict that the present epidemic of adolescent obesity in the United States will substantially increase future rates of adult CHD (19). In addition, there is already evidence that recent North American birth cohorts not only are becoming obese in greater number at a given age, but also earlier in their life course compared to the birth cohorts from the previous decades (20). Consequently this will lead to a greater cumulative exposure to excess weight over their lifetime, which will, most likely, have profound implications for future rates of obesity related co-morbidity (20). It is conceivable that a similar trend will occur in other western countries, dealing with an increased prevalence rate of childhood obesity during the last few decades. Importantly, the majority of overweight and obese adults in our time did not have overweight as a child. Therefore, the adult health risk profile of today's overweight youth might be different from that of earlier generations.

The epidemic proportions of childhood obesity support the idea of a population-based preventive approach. It is important to study, from a population-based view, the impact of lifestyle interventions on all children with obesity participating in these intervention and not only on those who complete the lifestyle intervention.

FUTURE PERSPECTIVES

The prevalence of obesity among children has been increasing since the 1980's, with little indication of a decrease or reversal of this trend (21). This has led to the prediction that today's generation of children may be the first for whom life expectancy falls (22). Although the knowledge of childhood obesity and its health consequences increases every year, many questions concerning best preventive and treatment possibilities remain still open. Preventing and treating childhood obesity has proven to be challenging and treatment options include lifestyle interventions (with or without psychological strategies), as well as pharmaceutical interventions and bariatric surgery (23). In general, the latter two treatment options are restricted to obese adolescents.

With today's knowledge, behavioral lifestyle interventions seem to be the preferred treatment strategy for obese children. Although most trials studying the effect of such interventions on childhood obesity show modest weight reducing results, the effect is statistically significant and clinically meaningful in reducing obesity and associated co-morbidity (1). In severely obese adolescents with obesity related co-morbidities, a more intensive weight loss therapy might be appropriate.

In a recent systematic review the role of pharmacotherapy in the treatment of childhood obesity was described, based on a meta-analysis (24). The pooled effect of both Sibutramine and Orlistat lead to a significant reduction in BMI of 2.4 kg/m^2 (CI 1.8, 3.1 kg/m^2) and 0.7 kg/m^2 (CI 0.3,1.2 kg/m^2), respectively, compared to placebo over 12 months (24). However, Sibutramine is no longer an option for young people with obesity in Europe as the license has been withdrawn because of cardiovascular safety concerns regarding its use in the adult population, although it still has a restricted license for use in the United States (25). Moreover, most drugs do not produce permanent changes in physiology or behavior, raising the prospect of life-long treatment (25). In addition, treatment effects of registered anti-obesity medication on weight reduction are modest as well (24). Taken together, adding medication as an adjunct to the lifestyle intervention can be considered, but this approach needs to be carefully weighted against the potential adverse effects (1).

Also the decision to advise bariatric surgery in obese adolescents should be taken with care. It can only be considered if intensive lifestyle interventions, possibly in combination with anti-obesity medication, have failed. In general, the laparoscopic adjusted gastric banding (LAGB) or Roux-en-Y gastric bypass (RYGB) lead to substantial weight loss in adults (26). Reliable data in obese adolescents on the effect of such procedures on weight reduction and the severity of side effects and complications of the procedures are lacking. Evidence so far is based on clinical observations. Short-term benefit of surgery in severely obese adolescent has been shown, but long-term follow-up data are sparse (25). Adverse events reported after surgery range from mild malnutrition to more severe complications, including severe malnutrition, gastrointestinal bleeding, and gastrointestinal obstruction (26). Therefore, in view of present knowledge, the surgical approach should be considered as a last resort for severely obese adolescents (27).

Future longitudinal research has to focus mainly on which child will benefit from which kind of intervention to develop specific individualized therapies, as well as straightforward changes of social environment by the government and local authorities in order to "detoxify" it. Meanwhile it is advised to try to motivate obese children to change their lifestyle and eating pattern, with the help of a dietician. Assessment of WC, physical fitness and HRQOL will assist the health professionals to achieve a better insight in the development of health risk of the obese child and may motivate the obese child and family during treatment.

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Chapter 8

Summary

8

8 Summary

Childhood obesity has become a global problem. The rapidly increasing prevalence of childhood obesity observed during the last few decades is assumed to be mostly the result of environmental factors such as increased food consumption and a change from a more physically active lifestyle to a more sedentary one. Childhood obesity affects self-esteem and has negative consequences on cognitive and social development. Obese children tend to become obese adults with increased risk for developing cardiovascular complications, type 2 diabetes mellitus and psychosocial problems. Additionally, the secretion of several gastrointestinal hormones, responsible for appetite and food intake, is altered in obese subjects. Understanding the mechanisms that control energy balance and fuel flux in children with obesity is of paramount importance for the design of effective strategies to combat this health hazard. So far, the most appropriate treatment for obese children is a multidisciplinary cognitive behavioral intervention. The results of such interventions immediately after treatment are promising. However, the intermediate- and long-term follow-up effects are largely unknown and indecisive.

8 Summary

The main objective of the studies presented in this thesis is the effect evaluation of a family-based cognitive behavioral multidisciplinary lifestyle treatment on childhood obesity. The intervention aims to establish long-term weight reduction and stabilization, reduction of obesity-related health consequences and improvement of self-image by change of lifestyle and education using cognitive behavioral techniques.

In this longitudinal clinical trial newly presented children with obesity (8-17 years old) were randomly attributed to an intervention or control group, both consisting of 40 children. The intervention was carried out in groups of 8-11 children, and consisted of 7 and 5 separate group meetings for the children and their parents, respectively, and 1 joint group meeting of 2½ hours. Main topics were education on nutrition, self-control techniques, social skills, physical activity and improvement of self-esteem. The control group was given advice on physical activity and nutrition. For comparison with non-obese peers, additional data were collected from 34 normal-weight children, 8-17 years old.

In **chapter 2** the study protocol of the family-based multidisciplinary cognitive behavioral treatment is extensively described.

The treatment effect of this family-based multidisciplinary cognitive behavioral lifestyle intervention on adiposity, physical fitness, glucose homeostasis and inflammatory state in obese children compared to standard care is presented in **chapter 3**. Our intensive lifestyle intervention resulted in a modest long-term reduction of both total and abdominal adiposity accompanied by improved physical fitness, while unchanged adiposity in untreated controls led to decreased physical fitness and deterioration of insulin sensitivity. No effect was observed on inflammatory markers.

In **chapter 4** it is shown that the observed weight reduction did not affect gut hormone concentrations, except that it significantly increased the postprandial ghrelin response after treatment.

Chapter 5 shows that Health Related Quality of Life (HRQOL) is significantly impaired in obese children concerning the physical activity and self-perception domains compared to their normal weight peers. The parents of obese children reported significantly lower HRQOL scores for their children compared to the estimates made by their children themselves. We found that our multidisciplinary lifestyle treatment was effective in improving the HRQOL of the obese children after 1 year.

In **chapter 6** we propose an alternative for the definition of the metabolic syndrome, since the usefulness of its current dichotomous form is questioned. We suggest the use of a prediction model for increased insulin resistance (defined as HOMA-IR), in which the different degree of the impact of the individual components of the metabolic syndrome is considered. In this chapter we show that this multivariate prediction model based on the individual components of the metabolic syndrome expressed as standard deviation scores (SDS) has a good predictive value for increased HOMA-IR SDS.

Chapter 9

Samenvatting
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Samenvatting

Obesitas (vetzucht) bij kinderen is gedurende de afgelopen decennia een groeiend en wereldwijd probleem geworden. De snel toenemende prevalentie van obesitas op de kinderleeftijd is voornamelijk te wijten aan verandering in omgevingsfactoren, zoals een toegenomen voedselconsumptie en de verandering van een actieve naar een meer inactieve levenswijze.

Obesitas heeft negatieve gevolgen voor het zelfvertrouwen en voor de cognitieve en sociale ontwikkeling van het kind. Daarnaast is gebleken dat dikke kinderen vaak dik blijven als volwassene, wat op zijn beurt samengaat met een verhoogd risico op het ontwikkelen van cardiovasculaire complicaties, diabetes mellitus type 2 en psychosociale problemen. Tevens wordt bij dikke volwassenen en kinderen een verandering waargenomen in de secretie van diverse maagdarm-hormonen, die een rol spelen in het reguleren van de voedselinname. Het is van groot belang om inzicht te verkrijgen in de mechanismen die verantwoordelijk zijn voor het regelen van de energiebalans, om zo effectieve strategieën te kunnen ontwikkelen voor de behandeling van dit belangrijke gezondheidsprobleem.

De tot nu toe meest geschikt gebleken behandeling voor obesitas bij kinderen is een multidisciplinaire cognitieve gedragsinterventie. Over de middellange- en lange-termijn effecten van een dergelijke behandeling bestaat echter nog onduidelijkheid. Het primaire doel van de in dit proefschrift beschreven studies is de effect-evaluatie van een multidisciplinair behandelprogramma bij kinderen met obesitas. Het doel van de interventie was het bewerkstelligen van een blijvende gewichtreductie en een verbetering van het gezondheidsrisicoprofiel en het zelfvertrouwen door middel van een verandering van leefstijl.

In dit longitudinale klinische onderzoeksproject zijn recent verwezen kinderen met obesitas, in de leeftijd van 8-17 jaar, via randomisatie verdeeld in een interventie- en controlegroep van elk 40 kinderen. De interventie werd aangeboden in groepen van 8-11 deelnemers. Er waren 7 aparte bijeenkomsten van 2½ uur voor de kinderen, 5 voor hun ouders en 1 voor kinderen en ouders samen. Gedurende de groeps-bijeenkomsten werden een gezond voedingspatroon en een lichamelijk actieve leefstijl aangeleerd middels cognitieve gedragsveranderings-technieken. De controlegroep werd alleen geadviseerd om meer te bewegen en gezonder te eten. In een additionele groep van 34 kinderen (8-17 jaar) met een normaal gewicht werden gegevens verzameld waarmee de gegevens in beide groepen obese kinderen konden worden vergeleken. Een uitgebreide beschrijving van het studieprotocol van het multidisciplinaire behandelprogramma is weergegeven in **hoofdstuk 2**.

Het effect van deze multidisciplinaire behandeling op de mate van obesitas, lichamelijke fitheid, glucose-homeostase en ontstekingsparameters, in vergelijking met het effect van standaard zorg, wordt beschreven in **hoofdstuk 3**. Ons multidisciplinair behandelprogramma liet een bescheiden effect zien op de mate van obesitas en lichamelijke fitheid. In de controlegroep werd echter geen enkel effect op de mate van obesitas waargenomen en een verslechtering van de lichamelijke fitheid en insuline-gevoeligheid. Er was geen waarneembare verandering van het behandelprogramma op ontstekingsparameters in het bloed.

Samenvatting

In **hoofdstuk 4** laten we zien dat de waargenomen gewichtsreductie na behandeling geen effect had op de nuchtere bloedspiegel van PYY en GLP-1, noch op de verandering van de concentratie van deze darmhormonen na een testmaaltijd. De stijging van de bloedspiegel van ghrelin na een testmaaltijd nam echter significant toe na behandeling.

In **hoofdstuk 5** is te lezen dat kinderen met obesitas hun eigen kwaliteit van leven significant slechter beoordeelden dan hun leeftijdgenootjes met een normaal gewicht. Daarnaast beoordeelden de ouders van obese kinderen de kwaliteit van leven van hun kind als lager dan de kinderen zelf deden. In dit hoofdstuk laten we zien dat ons multidisciplinair behandelprogramma de kwaliteit van leven van de obese kinderen na 1 jaar significant heeft verbeterd.

In **hoofdstuk 6** geven we een alternatief voor de definitie van het metabool syndroom, aangezien de bruikbaarheid van de huidige dichotome vorm bekritiseerd wordt. Ons voorstel is om een predictiemodel voor insuline-resistentie (HOMA-IR) te gebruiken, waarbij rekening wordt gehouden met het verschil in impact van de individuele gestandaardiseerde componenten van het metabool syndroom. In dit hoofdstuk tonen we aan dat zo'n model de obesitas-gerelateerde comorbiditeit beter voorspelt dan de huidige dichotome definitie van het metabool syndroom.

Dankwoord

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Dankwoord

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Curriculum Vitae

Rimke Vos was born on 31 March, 1982 Delft, the Netherlands. She attended secondary school (De Vrije School Den Haag) in The Hague and passed her exam in 2001. From 2001-2005 she studied Public Health at Maastricht University, with a major on Movement Science. During her study she did a research project at Aristotle University of Thessaloniki, Greece from September-December 2004. From January-June 2005 she performed a research project at the Wilhelmina Children's Hospital on the physical performance and quality of life of children with hemophilia. In August 2005, she received her master degree in Public Health at Maastricht University (cum laude). In April 2006 she started to work as PhD student at the Juliana Children's Hospital/ HagaHospital (The Hague). The PhD project 'The effect evaluation of a family based multidisciplinary cognitive behavioural treatment in children with obesity' was carried out in collaboration with the Departments of Pediatrics (Willem-Alexander Children and Youth Center) and Endocrinology & Metabolism of the Leiden University Medical Center, under the supervision of dr. E.C.A.M. Houdijk, Prof. dr. J.M. Wit and Prof. dr. H. Pijl. She has recently started to work as researcher at the department of Rehabilitation Medicine at the VU University Medical Center (Amsterdam) and as researcher at the department of Medical Decision Making at Leiden University Medical Center (Leiden).

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